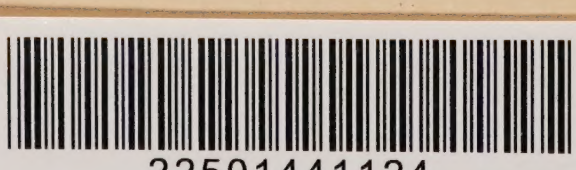
Notes on
Therapeutic Sera
Bacterial Vaccines
Etc.

Prepared by
The Lister Institute
of Preventive Medicine
London, S.W.1.

Issued under the authority
of the Governing Body

Printed and Published by the Sole Wholesale Agents:
Allen & Hanburys Ltd., London, E.C.3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1926

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injected, the resulting serum is an *antitoxic* serum, *i.e.*, it neutralises the poisonous action of the particular bacterial products.

In both cases the quantity of toxic material injected into the horse is at first very small, and is gradually increased until in some cases the animal receives, without ill-effects, an amount sufficient to kill a large number of unprepared horses.

The blood of the animal, which has thus been immunised, is collected in sterile vessels containing a solution of either potassium oxalate or of sodium citrate, in appropriate quantity, to prevent coagulation. When the corpuscles have settled down the supernatant plasma is siphoned off and clotted by the addition of a solution of calcium chloride. The serum removed from the clot constitutes the therapeutic agent, the antitoxic or anti-microbial serum.

The antitoxic sera may be refined and concentrated by chemical means. During this process the antitoxic globulins are separated from those proteins of the serum which do not carry a charge of antitoxin and are therefore of no value from a therapeutic point of view, while their removal is an advantage to the patient. The Diphtheria Antitoxin, Tetanus Antitoxin, Scarlet Fever Antitoxin, Anti-Dysentery Serum and Anti-Scorpion Serum sent out by the Lister Institute are so treated.

All serum is kept for a certain period during which the horse remains under observation : should any signs of illness appear, the serum is destroyed.

At the Lister Institute all sera are passed through germ-proof filters to ensure sterility. Prior to filtration there is added, in most cases, 0·3 to 0·5 per cent. of carbolic acid, or other preservative.

Before being passed for use each batch of serum is subjected to the following tests :

1. For sterility : the serum must be germ-free.
2. For absence of toxicity : 10 to 15 c.cm. are injected beneath the skin of a guinea pig, and the animal is kept under observation for 10 to 15 days. The animal must remain in good health.

In all sera there occurs, on standing, some deposit of proteins which renders the liquid turbid when shaken. Such a deposit is harmless except for intravenous injection, when it must be removed either by filtration or decantation. Sera should be stored in a dry, cold, dark place (at a temperature of from 32° to 40° F). Tests of those sera of which the potency can be estimated show that, when kept under proper conditions, they lose their potency slowly, at the rate of about 8 per cent. per annum.

In the case of antitoxic sera provision is made in each phial to allow for any loss which may occur during one or two years. It is necessary to remember that the loss is in the *quantity only* and not in the *quality* of the antitoxin, and may be compensated for by the administration of a correspondingly larger volume of the serum.

A bottle of serum once opened should on no account be laid aside for use on a subsequent occasion. Although a small amount of preservative is added to the serum, this is insufficient to prevent bacterial growth when gross contamination has occurred.

Technique of Injection.—The syringe must be well washed and boiled for 5 minutes before use. In performing the injection strict asepsis must be observed. The skin must be well cleansed with soap and water and afterwards treated with an antiseptic solution, or by painting with a 2 per cent. solution of iodine in alcohol or in chloroform. The needle fitted to the syringe should be inserted into the bottle, the neck of which has been previously broken at the file mark in the manner described in the circular.

It is always advisable to warm the serum to 99°—100° F. before injection. **This procedure must not be omitted in the case of intraspinal or intravenous administration.**

Subcutaneous Injection.—Where the injection is to be subcutaneous, the flank between the crest of the ilium and the last rib, or the lower part of the abdomen, is generally selected, but any region with loose subcutaneous tissue is suitable.

If it is necessary to use more than one syringeful, the needle should not be withdrawn, but the syringe merely detached and refilled.

Intramuscular Injection.—Serum is absorbed much more quickly when injected into muscular tissues than when given beneath the skin, the relative rates being about 8 hours and 48 hours. A convenient place for an intramuscular injection is about the middle of the outer side of the thigh, pushing the needle deeply into the *vastus externus* muscle, with the same precautions against infection as in subcutaneous injection.

Intravenous Injection.—The most convenient site for this injection is one of the large veins at the bend of the elbow. It is unnecessary to incise the skin; cleanse the site as for subcutaneous injection and place a few turns of bandage sufficiently tight round the arm to obstruct the venous circulation. Draw up the serum so as not quite to fill the syringe, and attach a sharp needle. Remove any air-bubbles from the syringe. Insert the needle into the vein, withdraw a little blood into the syringe so as to be assured that the needle is properly within the vein and, having removed the bandage, slowly inject the serum. If a larger quantity has to be introduced than the capacity of the syringe permits, place the finger gently upon the vein and disconnect, leaving the needle in the vein, whilst an assistant refills the barrel of the syringe. Great care must be taken to avoid injection of air into the vein.

If a deposit is present, the serum should be strained through a piece of linen, which has just been boiled, or the clear serum may be pipetted off from the deposit.

The advantage of the intravenous method is that the antitoxin is immediately available to neutralise the poison, whereas, when subcutaneous injection is employed, considerable delay ensues before the whole of the antitoxin introduced reaches the circulation.

C. J. Martin showed by experiments upon animals that anti-venom serum was at least 20, sometimes 100 times as effective, when administered into a vein, and Henderson Smith found that after subcutaneous injection of anti-diphtheria serum in man the maximum quantity of antitoxin was not present in the circulating blood until the third day. Moreover, the concentration in the blood never reached that obtained by introducing the same quantity directly into a vein. In the case of diphtheria eight hours are saved by intravenous injection —an important factor in a critical case.

Owing to the possible development of hypersensibility (anaphylaxis) to horse serum, the intravenous method should not be employed, unless the gravity of the symptoms justifies this risk, in cases where horse serum has been injected more than 14 days before, even if it be two years since the last injection was made. In such cases it is advisable to administer slowly a minute quantity of the dose (say 1 c.c. made up to 10 c.c. with sterile physiological saline) and after an interval of half-an-hour, if no untoward symptoms have developed, to inject slowly the remainder of the dose.

Diphtheria Antitoxin.

Diphtheria Antitoxin is the serum of horses which have been highly immunised against the toxin of the diphtheria bacillus. It possesses the power of rendering the toxin non-poisonous. The latter when present in the fluids of the body becomes attached more particularly to the cells of the circulatory, renal and nervous systems and adrenal bodies. In the very early stages of the disease comparatively small amounts of antitoxin suffice to bring about the desired separation of toxin from the cell and the neutralization of the toxin ; but as time goes on larger and larger quantities of antitoxin are required until there comes a time when even enormous amounts of antitoxin seem to be powerless to heal. This conclusion, which is based on experimental evidence, is borne out by the results of clinical experience in all parts of the world, as is shown by the following table, the details of which are culled from various sources.

TABLE I.

	Total No. of Cases	Total P'tage Mortality	Percentage Mortality when treatment began on					
			1st day	2nd day	3rd day	4th day	5th day	6th day or later
*Collective Investigation in Russia..	44,631	14·6	3·7	8·2	16·2	25·9	—	—
*Collective Investigation in Germany	9,581	15·5	6·6	8·3	12·9	17·0	23·2	—
*Collective Investigation in Austria	1,103	12·6	8·0	6·6	9·8	25·5	28·8	—
Deycke. Collected Statistics	78,028	15·2	4·3	7·6	14·7	19·7	31·6	31·5
Commonwealth of Pennsylvania Health Department, 1912	2,793	4·33	1·40	4·60	10·52	25·51	18·18	23·68
Commonwealth of Pennsylvania Health Department, 1913	45,030	7·98	5·18	8·75	14·94	22·51	24·96	29·10
Chicago Health Department, 1895-1906.. ..	8,372†	6·50	0·32	1·51	3·38	11·15	22·01	—
Metropolitan Asylums Board Report, 1908 ..	4,531	10·8	3·0	6·5	10·6	12·9	14·8	—
Metropolitan Asylums Board Report, 1911 ..	3,864	9·36	2·68	3·4	8·86	12·59	13·44	—

† Cases verified by bacteriological examination. * Cited by Dieudonné (1913).

So convinced is the Health Department of New York City, U.S.A., that the death-rate from diphtheria can be reduced by the administration of 5,000 units of antitoxin on the first day of the disease that it has offered to provide antitoxin free of cost for this purpose. It is not only the case mortality that is affected by the early administration of antitoxin but also the occurrence of paralysis. Rosenau and Anderson (1907), after a careful experimental study of the question say: "The fact that *one unit* of antitoxin prevents paralysis and saves life when administered timely, whereas *4,000 units totally fail* when delayed 48 hours, emphasizes the importance of using this sovereign remedy early." Here again clinical experience bears out the conclusion formed in the laboratory, as may be seen in the following table drawn up by J. D. Rolleston (1913):

TABLE II.

Day of disease on which serum treatment was begun.	Total No. of cases injected.	Paralysis cases. Percentage.	Severe forms only. Percentage.
First day	83	3·6	0
Second day	461	14·09	3·9
Third day	541	21·4	7·5
Fourth day	460	26·9	10·0
Fifth day	304	26·3	13·4
Sixth day	166	27·1	12·6
Seventh day	215	18·6	7·9
Total	2,230	21·21	8·2

It is evident that the giving of serum early in the disease has a distinctly favourable influence on the prognosis both as regards case mortality and the incidence of paralysis, more especially of the severer forms. Other reasons for instituting serum treatment as early as possible are that convalescence is more quickly established and that a dose of antitoxin given early has a greater effect than a much larger dose given later in the disease. Thus by beginning serum treatment early in the disease there is a fourfold economy, viz,: in

1. Life—in that the case mortality is greatly reduced.
2. Health—in that complications and troublesome sequelæ are minimised.
3. Time—in that convalescence is more rapidly established.
4. Money—in that an adequate dose given early has a greater effect than many times the same dose given later.

Method of Use: Antitoxin may be given subcutaneously, intramuscularly or intravenously. The first is the slowest route, as the maximum antitoxin content in the blood is not reached until after the lapse of two to three days, whereas after intramuscular injection the maximum is reached in about twelve hours, and after intravenous injection in a few minutes.

The experiments of Berghaus (1909) working in Ehrlich's laboratory, indicate that the curative value of antidiphtheritic serum is 500 times as great when given intravenously as when given subcutaneously. W. H. Park (1913), from clinical experience thinks that 5,000 units given intravenously is equal to 20,000 units given subcutaneously. Therefore, in urgent cases when there is severe toxæmia, antitoxin may be given intravenously. But on account of the greatly increased risk (viz., that of anaphylactic trouble occurring) which attaches to intravenous inoculation, it is better in ordinary cases to give serum by the intramuscular route—the absorption is rapid and the concentration of antitoxin in the blood reaches a higher point than when given subcutaneously and remains high for a longer time than after intravenous injection. Subcutaneous inoculation should be used only when it is required to supplement the other methods, or when the serum is given for prophylactic purposes. Whichever method is used every precaution should be taken to prevent infection occurring from the skin of the patient, from the instruments, or from the hands of the operator.

Dosage: The dose to be given entirely depends upon the severity of the case, and it must be remembered that it is not always possible at the beginning of treatment to obtain from the character of the attack a correct appreciation of the severity of the intoxication. Thus Purdy reports a case in which a most careful scrutiny failed to discover any membrane at the first examination, but next day the membrane covered the tonsils, posterior pharynx, uvula and nasal cavity, and the case rapidly progressed to a fatal issue.

The scale recommended in 1913 by Rolleston and MacLeod (Metropolitan Asylums Board Reports) is as follows—it being understood that the antitoxin is given intramuscularly, and that the dose is repeated when necessary:—

Mild faucial	4,000-8,000 units.
Moderate faucial	8,000-12,000 ,,
Severe faucial	16,000-20,000 ,,
Nasal or laryngeal, without faucial	4,000-12,000 ,,

S. S. Woody *(Jour. Amer. Med. Assn.*, 1914, vol. 63, p. 861), from a personal observation of over 10,000 cases of diphtheria, at the Philadelphia Hospital for Contagious Diseases, is of opinion that diphtheria antitoxin is given in doses which are far too small. He thinks that every case should have not less than 10,000 units. It both tonsils are covered with exudate of 1-2 days' duration the dose should be 30,000-60,000 units, and if the palate, uvula and nose are also involved for three days or more 150,000-300,000 units should be given. Simple nasal diphtheria requires 20,000 units, but if there is also marked toxæmia 50,000-150,000 units. The doses may seem very large, but there is no doubt that of recent years the tendency has been to give doses distinctly larger than those that formerly were considered sufficient.

L. H. South (*Jour. Amer. Med. Assn.*, 1920, Vol. 75, p. 1225), favours an initial dose of 10,000-20,000 units, and expresses the opinion that if antitoxin be given on the first day of the disease in adequate doses there will be no deaths.

J. de Toledo Pisa (*Annaes Paulistas de Med. e Cir. S. Paolo*, 1919) states that a study of the cases of diphtheria at S. Paolo, during the preceding ten years, shows a constant decline in the death rate as the doses were progressively increased. He recommends 10,000-30,000 units, and considers that fractioning the dose is annoying to the patient and less effectual than a single large dose.

There is much to be said for this latter procedure. If a large dose be given at first there is a rapid neutralization of the toxin already present, and an excess is left over in the body to meet any future needs as they arise and before any further harm can be done.

W. H. Park (1913), who, as Director of the Hygienic Laboratory of the New York Health Department, has had a very large experience, is distinctly in favour of giving in one dose all the antitoxin judged to be necessary for the case.

Fred. H. Thomson (Medical Superintendent N.E. Fever Hospital of the Metropolitan Asylums Board), in *The Lancet*, July 9th, 1921, p. 68, says that, "ideally, the amount of antitoxin necessary should be administered in one dose, but it is very difficult to estimate the quantity, and so second doses are often required. It is desirable that the second dose should be given not later than twenty-four hours after the first. Repeated doses extending over a few days are not to be recommended." He further says that it is very difficult to estimate the doses in any given case, and the only safe method appears to be to err purposely on the ample side. Personally, he would not care to give less than 6,000 units, and he would advise all those who are uncertain that the case is really a mild attack never to give less than 8,000 units. He considers it impossible to say what the maximum necessary dosage is in the most severe cases. Some cases in his experience have seemed to need more than 50,000 units. He suggests the following doses :—

TABLE III.

	If Treated on 1st Day.	If Untreated, until— 2nd Day.	3rd Day.	4th Day.
Mild faucial	6,000 units	6,000 units	8,000 units	10,000 units
Moderate faucial	10,000 „	12,000 „	14,000 „	16,000 „
Severe faucial	20,000 „	24,000 „	30,000 „	30,000 „
Severe faucial + laryngeal				
Very severe faucial ..	30,000 „	40,000 „	50,000 „	50,000 „
Laryngeal only	18,000 „	18,000 „	18,000 „	18,000 „
Nasal only, but with membrane	6,000 „	6,000 „	6,000 „	10,000 „
Conjunctival only.. ..				

These doses are to be given intramuscularly, and a further dose in twenty-four hours if no improvement has taken place.

Now, if we study the Metropolitan Asylums Board Reports for the last ten years we find, as shown in the following table, that the average amount of antitoxin given to each of some 80,000 patients has been some 17,000 units, and, bearing in mind that we can never predict how an attack of diphtheria will develop, it would seem to be a not unreasonable procedure to inject this average dose of some 17,000 units as soon as it has been decided to administer antitoxin, and this decision should be made as soon as the clinical condition warrants it, and without waiting for the results of a bacteriological examination :—

TABLE IV.

Year.	No. of Cases.	Average No. of Units given to each patient.	Percentage Mortality.	Percentage Paralysis.
1909	5,610	14,751	9·44	13·94
1910	4,502	14,835	7·83	13·43
1911	6,127	17,328	8·90	11·15
1912	6,510	14,871	6·57	9·38
1913	6,283	17,113	6·63	7·85
1914	8,101	18,240	8·47	8·76
1915	8,172	19,559	8·42	Not published.
1916	8,479	16,607	7·19	
1917	8,090	16,548	7·20	
1918	8,041	19,445	8·14	
1919	8.164	18,367	9·27	
1920	12.285	19,788	8·61	

General Remarks : *Paralysis.* Meyer and Kayser both suggest that the habitual use of alcohol may be a predisposing cause of diphtheritic paralysis.

Cardio-vascular Failure. Creutzfeldt and Koch state that in seven out of nine cases of death from cardio-vascular failure during diphtheria they found profound changes in the pituitary body and that they could reproduce these changes in guinea-pigs by injections of pure cultures of diphtheria bacilli. They, therefore, recommend pituitary-adrenalin therapy in this condition. In this connection a remark of Rolleston's (1913) is of interest. He says "The occurrence of a well-marked serum reaction at the usual period after injection is of favourable omen, it being most exceptional for those cases to die from cardiac paralysis in whom an urticarial eruption has been well developed."

Joint Pains and Rashes. Joint pains and rashes of various types accompanied by a rise of temperature sometimes occur after the injection. These need cause no apprehension.

Intravenous Injection. When intravenous injection is considered necessary it should be noted that before giving the injection it is advisable to make enquiry as to previous injections of serum and whether the patient has any idiosyncrasy (such as liability to attacks of asthma, to be affected by emanations from horses, etc.), because the risk of anaphylactic trouble occurring is distinctly greater after intravenous than after intramuscular or subcutaneous injection.

Keeping qualities. Stored in the dark and in a cold place—an ice chest—Diphtheria Antitoxin retains its potency very well, and under these conditions (darkness and 3°C.) the annual loss is on the average about 8 per cent. The higher the temperature the greater the loss. At 36°C. the loss may be 50 per cent. in six months. It is to be noted that the loss is in *quantity* only. The *quality* of the antitoxin remains the same but there are fewer units in a bottle. Usually there is put in each bottle an excess of units sufficient to compensate for the average loss during two years.

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Tetanus Antitoxin.

The tetanus bacillus is widely distributed in nature. It is a normal inhabitant of the intestine of cattle and horses and is found in the soil of most cultivated areas, in the streets of cities, and in fact in any place where there is fæcal contamination. It has been met with frequently in the wads of blank cartridges and fireworks, which contain the uncleaned hair of animals, and wounds by these wads are therefore dangerous.

Antitetanic Serum (Tetanus Antitoxin) is the serum of horses which have been highly immunised against the toxin of the tetanus bacillus. Of recent years it has been suggested that there are several types of the tetanus bacillus. Representatives of all the suggested varieties are used in the preparation of the Lister Institute Serum.

Method of Use : When using serum every precaution should be taken to prevent infection from the skin of the patient, from the instruments or from the hands of the operator. Except in the case of a small prophylactic dose *serum must always be warmed to body heat before injection.*

Prophylactic Use: Experience, both clinical and experimental (MacConkey, *Brit. Med. Journal*, Dec. 11th, 1915; MacConkey and Hower, *Lancet*, Feb. 17th, 1917), has proved beyond all doubt the value of Tetanus Antitoxin when used " prophylatically." Employed in this way it is an almost unfailing remedy against tetanus. Consequently it cannot be too strongly emphasized that every person who receives a wound in which there is any likelihood of infection with the *Bacillus tetani* should have administered, as part of the treatment, a prophylactic injection of Tetanus Antitoxin.

It has been shown experimentally that, within limits, the larger the dose of antitoxin the longer is the duration of the "passive immunity" conferred thereby and therefore it is advisable to give a dose which errs on the ample side. Five hundred units (U.S.A. standard) is the smallest amount which should be given, but it is better to give 1500-3000 units or even more when a wound is much contaminated or where there is much dead tissue in a wound which is several days old before it comes under observation. If it is proposed to operate in such a case the antitoxin should be given intramuscularly 3-6 hours, if possible, before any attempt is made to clean out or scrape the wound. This recommendation is made in view of the fact that acute tetanus has occurred within 24 hours of such operations and has apparently been due to the rapid absorption, by the fresh tissues laid bare by the operation, of toxin which had been elaborated in the necrotic tissues.

Tetanus Antitoxin can neutralise tetanus toxin, but it cannot prevent the growth of the bacillus and so, as the tetanus bacillus can multiply and produce toxin in blood clots, in sequestra, or in necrotic tissues, especially in the depths of a wound, it is of great importance that all such loci of growth should be removed. When removing a foreign body any fibrous capsule which encloses it should also be dissected away.

In view of the known destructive action of iodine on tetanus toxins the use of solutions of iodine or of iodide of starch in the local treatment of such wounds is indicated.

Prophylactic injections should, as a rule, be given under the skin of the abdomen or flank. If a more rapid absorption is desired the injection should be made intramuscularly—on the outer side of the thigh into the body of the *vastus externus* muscle.

Curative Use: Experiment has shown that if Tetanus Antitoxin be given in sufficient amount soon enough after the injection of a lethal dose of tetanus toxin a fatal issue can be avoided; but if the administration of antitoxin be delayed beyond a certain time death cannot be prevented.

The serum treatment of tetanus is unsatisfactory because there are no definite early signs of the disease such as, for instance, the formation of membrane in the case of diphtheria. It is only when the toxin has already affected the nerve centres that muscular spasms occur. It is also doubtful to what extent the damage done to the nerve cells can be counteracted by antitoxin. Consequently time is the all important element in the treatment of tetanus and the delay of an hour in the institution of active treatment may make all the difference between success and failure. The moment that any manifestations of tetanus are observed no time should be lost before beginning energetic specific treatment.

In acute tetanus the object should be to flood and saturate the system with antitoxin as quickly as possible. For this purpose 16,000-20,000 (U.S.A.) units of antitoxin should be injected beneath the spinal arachnoid (in the usual site for lumbar puncture) and the same amount should be given intramuscularly (on the outer side of the thigh into the body of the *vastus externus* muscle). If the condition of the patient is no better at the end of 12-18 hours these doses should be repeated and may be given once a day for 3-4 days if necessary, after which the administration may be confined to the intramuscular route in daily doses of 8,000-16,000 units. When improvement sets in the amount of antitoxin given each day may be gradually diminished and given subcutaneously until all fear of a relapse is past. *But it must not be forgotten that a patient is never out of danger, even though the wound may be completely healed, as long as any foreign body (bit of metal, of clothing, sequestrum of bone, etc.) remains in the body.* Tetanus bacilli have been found as late as 882 days after the reception of the injury (War Office Memorandum on Tetanus, 4th Edition, 1919, p. 6). In another case (Lumière, 1916, Compt. Rend. Acad. d. Sciences, 163, p. 378) tetanus bacilli were found on a bullet removed from the body of a soldier, who had *not* had tetanus, 38 days after the wound and 15 days after cicatrization.

In local or chronic tetanus 1,500-3,000 units may be given subcutaneously every few days but if any signs of extension occur then active treatment should be begun at once.

Lumbar Puncture: The serum when ready for injection must be ***at blood heat.*** The needle which should be about 1 mm. in diameter and about 9 cm. long, should, if not already sterile, be boiled in sodium carbonate solution or other liquid that will not dull the point. Throughout the operation every precaution should be taken to maintain asepsis.

The patient should preferably be under general anæsthesia.

The patient is placed head to knees presenting to the operator a back as fully bent as practicable so as to separate the spinous processes of the vertebræ to the greatest extent.

A line joining the highest points of the iliac crests usually passes across the spinous process of the 4th lumbar vertebra. Just below the point of this process the thumb or index finger should be pressed in between the processes and the point of the needle entered on a level with the finger and a little to one side of it, directed upwards and inwards towards the middle line (so as to strike the middle line at the dura mater) and pushed steadily forward until the resistance at the ligament between the vertebral laminæ is encountered. This ligament may offer some resistance to penetration—may give the sensation of passing through a substance of cartilaginous consistency. Then the dura mater and arachnoid, reached, in the adult, at a depth of some 6 cm. are easily traversed and the cerebro-spinal fluid escapes.

(If puncturing in the middle is preferred it is as well to remember that in the adult the interspinous ligament may be very hard.)

Should no fluid escape, the needle may have become blocked or may have failed to enter the subarachnoid space. Then it may be necessary to pass a stylet, to withdraw the needle a little and then push it in in a slightly different direction, or to withdraw it completely and puncture through another space. When as much cerebro-spinal fluid as it is considered advisable to withdraw (about 20 c.cm. in adults) has been collected and measured the needle is connected to the serum container and the serum run in very gently and slowly. The quantity of serum injected should not be larger than the amount of cerebro-spinal fluid withdrawn.

The site of the operation should be kept **dry.** The bed should be tilted at the foot and the pillow removed for an hour or two after the injection.

The amount of preservative in the antitoxin is not likely to have any bad effect when the serum is given intraspinally.

The introduction of serum into the subarachnoid space always produces turbidity of the cerebro-spinal fluid, due to polymorphonuclear leucocytosis ; this reaction is sometimes associated with transient symptoms of meningeal irritation, which need cause no alarm (War Office Memorandum, p. 10). Erythematous and other rashes and joint pains may appear from 4 days to 5-6 weeks after the injection. They need cause no apprehension.

"Premonitory" Symptoms of Tetanus : As success in the treatment of tetanus depends so much upon the institution of specific treatment at the earliest possible moment and as commencing tetanus has been mistaken for sore throat, mumps, rheumatism, &c., it behoves us to be on the alert to detect any signs or symptoms which may arouse our suspicions that we have a case of tetanus to deal with.

Evler (Deutsch. Med. Wochensch., 1910, p. 961, quoted in Brit. Med. Jour. Oct. 10, 1914, and in Jour. R.A.M.C., March, 1916) gives the following list of symptoms some or several of which he has observed to precede the onset of tetanus and which he regards as premonitory of this disease :—General restlessness changing suddenly to a desire for rest and *vice versa.* Increased nervousness and unreasonable outbursts of temper. Sleeplessness, distressing dreams, nightly delirium, temporary giddiness, violent headache, excessive yawning. Diffuse backache. Trembling of the tongue which is put out to one side. Local swelling, without redness, of the injured member and throbbing of its arteries, notwithstanding that the limb be raised. Slight jerking following pressure on the flexor tendons and increased irritability of the muscles. Profuse sweating and darting pain in various parts. Difficulty in micturition, due to spasm of the sphincter vesicæ,

lasting from a few minutes to half an hour. Changes in the facial appearance—anxious look though there is as yet no *risus sardonicus*. Increased flow of saliva. Spasmodic cough. Earache. Stiffness at angle of jaw. Difficulty in swallowing. Tremors and clonic spasms, *which are not painful and may not attract attention.* Pain persisting after muscular contraction induced by effort. Evler thinks that the appearance of such symptoms after a wound that might have been infected with tetanus bacilli should prompt us to consider the administration of Tetanus Antitoxin.

Scarlet Fever Antitoxin.

This preparation is the serum of horses which have been immunised against the Streptococcus from scarlet fever. It contains not more than 0·4 % phenol or 0·35 % trikresol as a preservative.

Historical : The history of Scarlet Fever Antitoxin is most interesting and instructive. With the discovery and curative application of Diphtheria Antitoxin and Tetanus Antitoxin hopes were raised that therapeutic sera against other diseases would soon be forthcoming, and the widespread occurrence of infections due to streptococci directed attention to these organisms and attempts were made to prepare an anti-streptococcus serum.

Marmorek (1895) used such a serum in the treatment of erysipelas, puerperal fever, and other streptococcal infections, with apparent success. Later (1896) he thought that, though we did not know the microbe which causes scarlet fever, yet, as there was no doubt about the importance of the rôle played by the associated streptococci, anti-streptococcus serum should be given a trial in this disease. He came to the conclusion that it not only hindered grave complications but brought about an improvement in the general condition. The pulse slowed and became stronger, and the swollen glands diminished in size. He formed the opinion that, when the elevation in temperature was due to the streptococcus, it fell considerably on the injection of the serum, but that fever due to the virus of scarlatina continued and the eruption progressed as usual. These observations led to the conclusion that scarlet fever was not caused by the streptococcus as he knew it.

H. Aronson (1902) also introduced an anti-streptococcus serum but it did not give such good results as those recorded by P. Moser (1902). Moser believed that the streptococcus so frequently found in scarlet fever might be a special variety, and that to prepare a serum for use in the disease it was necessary to use the "special" variety of coccus isolated from fatal cases of scarlet fever. He thought there was an intoxication as well as an infection, and that a "specific" Anti-Streptococcus Serum might influence the intoxication and the infection at the same time. He prepared a multivalent serum on these lines and treated with it 81 out of 699 children with scarlatina, injecting doses of 30-180 c.cm. at one time. The case mortality was 9% as compared with 13% in

the untreated. The results improved as he used bigger doses, and also perhaps the later batches of serum may have been stronger. The serum had a quick and favourable influence on the general condition. The temperature and pulse often showed a rapid fall, and the chest and abdominal symptoms passed away usually within 24 hours. Moser emphasised the importance of large doses of serum. He isolated streptococci from the heart-blood of 63 out of 99 fatal cases of scarlet fever, and mentions that these organisms were seldom pathogenic for rabbits except in very large doses.

Moser's serum was used by Escherich (1903) the dose being 100-200 c.cm. given subcutaneously. He found that the serum showed, after a latent period of from 4-12 hours, a distinct influence on the symptoms due to intoxication, and because of this and of the early effect he considered it to be an antitoxic serum. He considered that a full dose should be given at once, and then a second injection would seldom be required. If given early in the disease the serum lessened the incidence of complications, but it had no effect upon the complications already present. Escherich also came to the conclusion that there were distinct indications that the streptococcus of scarlet fever was a specific variety. Moser's serum was also used by Kolly (1904), Bukowski (1905), Bokay (1905), Sserebrenekowa-Glinskaja (1905), and by Menschikoff (1905), who also used a serum prepared by Ssawczenko (1905), along Moser's lines. The descriptions given by these clinicians of the effects of the administration of the serum are the same as Moser's. Schick (1905) recommended the use of a strong serum in scarlet fever and regretted that, unfortunately, the strength of a serum could only be determined by the results which followed its administration in the human subject, and that we were entirely dependent on clinical observation.

In 1905, then, the position was that an Anti-Streptococcus Serum prepared by using streptococci isolated from fatal cases of scarlet fever had given good curative results in the hands of several observers, but that others had reported a want of success. There was no laboratory test by which the strength of various batches of serum could be compared, and it is obvious that unless this could be done there was no explanation for the failures which were reported of serum treatment. For instance, Jassny and Mizkewitz (1905) reported that they tried in 18 cases of scarlet fever an Anti-Scarlatina Serum prepared in the bacteriological station at Charkow. It was given in doses of 200-300 c.cm. and there were ten deaths. In neither the fatal cases nor in those who recovered could the slightest beneficial effect be attributed to the serum. It was only in eight other cases in which Moser's serum was used that serum treatment had any success, and in these the serum appeared to influence favourably the temperature, pulse and general condition, and to a somewhat less extent the throat symptoms.

In 1906, Gabritschewsky carried the subject a step farther. He reasoned that though every streptococcus cannot be called a scarlet fever coccus, yet, the fact that there is a disease of

horses which is caused by a streptococcus, and which has many symptoms that remind us of scarlet fever, is at least in favour of the possibility of a similar causation of the similar disease in human beings. His study of the effect of a vaccine in the cases of horses led him to prepare, with streptococci isolated from cases of scarlet fever, a vaccine for use in man. This vaccine was given to 700 children with good results, as regards the prevention of scarlet fever. Langowoi, who inoculated some of the children, noticed that in 13% of 120 vaccinated there occurred a punctiform exanthem resembling very closely the rash of scarlatina, but there was no desquamation. In some cases there was also an angina and, more seldom, vomiting, and sometimes a "strawberry tongue." Gabritschewsky thought there was a "toxin" effect, and no doubt he would have elucidated this point, but, unfortunately, death put an end to his studies.

Owing to the divergence of opinion among the clinicians, and to the absence of any means by which the streptococcus of scarlatina could be differentiated from other streptococci, neither the serum nor the vaccine came into general use, and we find Besredka (1912) expressing the opinion that, though the streptococcus was very frequently associated with scarlet fever, still there was no doubt, whatever, that it was *not* the causal agent of this disease and that Moser's serum was not a specific serum. He might have expressed a similar opinion about the serum of patients convalescent from scarlet fever. Since about 1896 such serum had been used in the treatment of cases of scarlatina. The effect varied, being sometimes beneficial, sometimes indifferent. In the former case the good influence was just the same as when Moser's serum was used. The irregular results in both cases were no doubt due to there being no method of standardizing the serum and thus ensuring proper dosage.

In 1918 Schultz and Charlton drew attention to the reaction which bears their name. If 0·5-1·0 c.cm. of the serum of a patient convalescent from scarlet fever be injected into the substance of the reddened skin of a person with a scarlatinal rash there occurs, in the course of a few hours, a blanching of the skin over the site of the injection and this blanching persists. Mair (1923) from his studies, concluded that this "extinction effect" was brought about by antitoxin in the blood of the convalescent.

In 1923 the Dicks succeeded in producing scarlet fever in one out of five volunteers whose throats were swabbed with a culture of a streptococcus isolated from a case of scarlet fever. They also showed that the infecting agent was not a "filtrable virus." Further, they introduced a susceptibility test on the lines of the "Schick" test. In 1924, Dochez prepared an Anti-Scarlatina Serum in the horse by using whole cultures of Scarlet Fever Streptococci, and the Dicks showed that an anti-serum could also be obtained by the injection of toxic filtrates. Since then similar sera have been prepared and used in England.

Such sera have been found to produce the "extinction phenomenon" just as convalescent Scarlet Fever Serum does, and after their administration a "Dick" test which previously has been positive gives a negative result. For reports as to the effect of the therapeutic administration of Scarlatina Antitoxin we are obliged to rely mostly on foreign sources, as the type of scarlet fever met with in England at the present time is usually so mild that it is difficult to estimate the effect of serum treatment. Given early, in adequate doses, in uncomplicated cases, the most striking effects are: Fall in the temperature and in the pulse rate within 4-12 hours, fading of the rash, subsidence of the angina, disappearance of the toxic manifestations (delirium, insomnia, etc.), and marked improvement in the general condition. Complications are prevented, but the serum has little or no effect upon complications already established. It is imperative, therefore, that the serum should be given as early as possible.

It will be noticed that the effects stated to follow the administration of the present day Scarlet Fever Antitoxin are the same as those attributed to Moser's serum. A link between the present and the past is furnished by Rosen and Korobicina (1925), who applied the "Dick" test to three cases to which Moser's antitoxic serum had been given. A negative reaction occurred in each case. The interesting point is that in one of the cases a "Dick" test had been performed before the administration of the serum, with a positive result.

The work of the Dicks and others in America has lifted the fog which enveloped the question of an Anti-Scarlatina Serum, and thrown a flood of light on the subject of scarlet fever.

Unfortunately the "Dick" test and its neutralization by means of serum can only be performed on the human subject, on susceptible persons who have never had scarlet fever. A regular and adequate supply of the proper kind of person is practically impossible to obtain and, as up to the present, no laboratory method of testing has been developed, the standardization of Scarlet Fever Antitoxin presents a problem full of practical difficulties.

Directions for Use: The syringe and needle should be boiled for five minutes immediately before use. Before injection the skin must be well washed with soap and warm water, and then with carbolic acid (1 in 20) or painted with 2% solution of iodine in chloroform, or in rectified spirit.

The serum should be given as early in the attack as possible.

From 40-80 c.cm. or in severe cases even more of the whole serum should be given as a single dose. Of concentrated serum a *correspondingly smaller* amount should form the dose. It is advisable to give an adequate amount at first and thus avoid a second injection, but should the symptoms return then the dose should be repeated.

The most rapid effect of serum is seen after intravenous injection, but owing to the greater risk should anaphylaxis occur after this mode of administration, it is preferable to inject the antitoxin into the muscles (*e.g., vastus externus*). In very severe cases the danger of the disease may outweigh the risks of intravenous dosage.

It is advisable to *warm* the serum to blood heat before injection, and in the case of intravenous administration this is *absolutely imperative.*

Erythematous and other rashes and joint pains may appear from four days to five to six weeks after the injection. They need cause no apprehension.

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Anti-Streptococcus Serum (Multivalent).

Opinions are divided as to the value of Anti-Streptococcus Serum as a therapeutic agent. In some cases the injection of serum is followed by a marked improvement in the condition of the patient, while in others no amelioration of the symptoms occurs. These varying results have been explained as being due to the fact that there are many races of streptococci, and that the serum prepared by the employment of one race only (univalent serum) may not necessarily antagonise another race of the

coccus. To minimise this difficulty a large number of races of streptococci is used in immunising the horses, and thus a multivalent serum is obtained. In the preparation of the serum supplied by the Lister Institute at least 50-100 races of streptococci (hæmolytic, non-hæmolytic and fæcalis) are employed. These are obtained from a large number of forms of streptococcal infection, *e.g.*, erysipelas, septicæmia, endocarditis, uterine infections, influenza, appendicitis, etc.

This serum contains not more than 0·4% phenol or 0·35% cresylic acid.

Method of Use : The syringe and needle should be boiled for five minutes immediately before use.

Before injection (usually made under the skin of the abdomen or flank) the skin must be well washed with soap and warm water, and then with carbolic acid (1 in 20) or other disinfectant, or painted with a 2% solution of iodine in chloroform or in rectified spirit. Local injections into the primary focus have also been recommended.

In an acute case 30 c.cm. should be given at once and may be repeated every six hours if necessary. Some authorities advise much larger doses, 100 c.cm. or even more.

Erythematous and other rashes, and joint pains, may sometimes appear from four days to five or six weeks after the injection. These need cause no apprehension.

Anti-Meningococcus Serum.

(This Serum contains not more than 0·5% Phenol or 0·35% Cresylic Acid.)

Anti-Meningococcus Serum is the serum of horses which have been immunised against the *Meningococcus intracellularis* (Weichselbaum). In the preparation of the Lister Institute serum many strains of the organism are used. It is, therefore, a multivalent serum. When first used Anti-Meningococcus serum was given subcutaneously, and it proved a failure. Its full effect was not obtained until it was injected intraspinally by lumbar puncture, which is the method now used for its administration. The serum is put up in doses of 10 c.c., 15 c.c. and 30 c.c., contained in ampoules of a shape which is specially adapted to its administration by the gravity method.

Dosage : In ordinary cases the routine dose of serum for adults should be 30 c.c., except when a smaller amount of fluid has been withdrawn. If the amount of fluid withdrawn and the condition of the patient during the injection allow of it the dose may be increased up to 45 c.c. The dose should be repeated at intervals of 24 hours *for at least four days*, later injections being regulated by the condition of the patient. A recurrence of the infection is much less apt to occur if one or two injections of serum are given after an examination of the spinal fluid has shown the absence of organisms. In the case of children under

five years of age it is inadvisable to inject a larger dose than 10 c.c., and the amount of cerebro-spinal fluid withdrawn may afford some indication as to the size of the dose. In severe and fulminating cases the dose of serum should if possible be 45 c.c., which may be given twice in the first 24 hours and later at 24 hour intervals. After the serum has been injected the patient should lie with the head and shoulders low and the pelvis raised.

Lumbar Puncture: Throughout the operation every precaution should be taken to maintain strict asepsis of the hands of the operator, of the skin of the patient, of the instruments, and of the serum. ***The serum when ready for injection should be at blood heat.*** The needle, which should be about 1 m.m. in diameter and about 9 cm. long, should, if not already sterile, be boiled in sodium carbonate solution or other liquid that will not dull the point. It is necessary to have an assistant to support the patient and to prevent his making any brusque movement which might interfere with the success of the operation.

Local anæsthesia by ethyl chloride proves a convenience in some subjects. For very restless patients or cases with obstinate opisthotonos resisting forward bending of the spine an injection of morphia may be necessary, and in some cases a general anæsthetic cannot be avoided. Some authorities consider general anæsthesia to be dangerous, while others think that the dangers have been exaggerated. The patient should lie on the side with the knees drawn up against the abdomen and the head bent to the knees, presenting to the operator a back as fully bent as practicable, so as to separate the spinous processes of the vertebræ to the greatest extent.

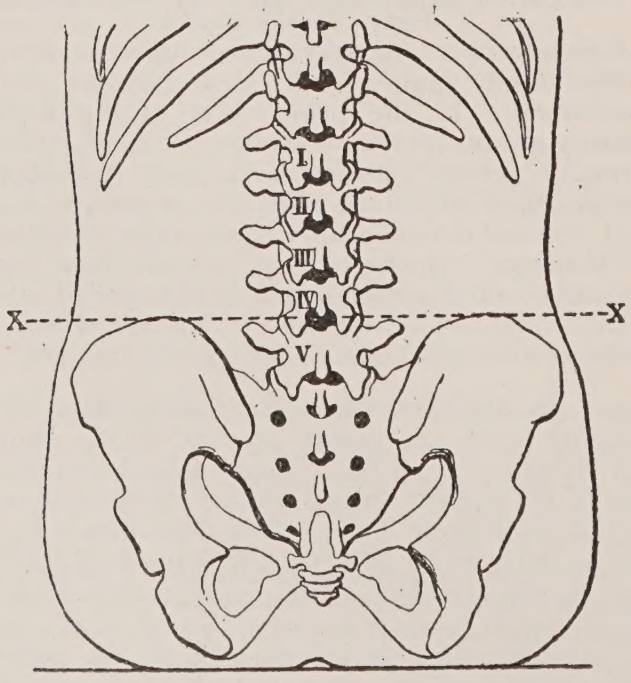

FIG. 1

A line joining the highest points of the iliac crests usually passes across the spinous process of the fourth lumbar vertebra. Just below the point of this process the thumb or index finger should be pressed in between the processes and the point of the ne dle entered on a level with the finger nail and a little to one side of it, directed upwards and inwards towards the middle line (so as to strike the middle line at the dura mater) and pushed steadily forward until the resistance of the ligament between the vertebral laminæ is encountered.

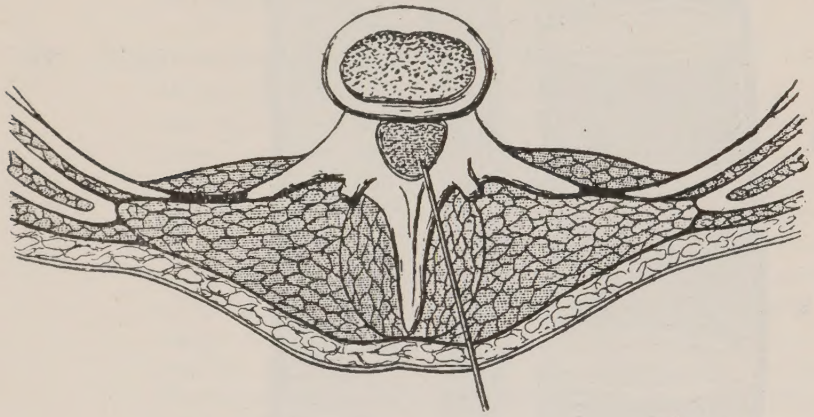

FIG. 2

This ligament may offer some resistance to penetration—may give the sensation of passing through a substance of cartilaginous consistency. Then the dura mater and arachnoid are, at a depth in the adult of some 6 cm., easily traversed and the cerebro-spinal fluid escapes. (If puncturing in the middle line is preferred it is necessary to remember that in the adult the interspinous ligament may be very hard.)

Should no fluid escape, the needle may have become blocked or may have failed to enter the subarachnoid space, in which case the injection cannot be carried out properly. Then it may be necessary to pass a stylet, to withdraw the needle a little and then push it in in a slightly different direction, or to withdraw the needle completely and puncture through another space.

When as much cerebro-spinal fluid as it is considered advisable to withdraw has been collected and measured the needle is connected to the serum container by means of a sterile rubber tube and the serum run in very gently and slowly by the gravity method under the least possible pressure.

Hirsch (1913, 2 cases) and Aubertin and Chabanier (1915, 50 cases) state that previous to injecting the serum they have washed out the subarachnoid space with warm saline, and that the beneficial influence of this lavage was apparent. This procedure has, however, not become general. Its chief use would be in cases with thick purulent fluid.

"In case of a 'dry tap,' serum should be given with the utmost caution, introducing it very slowly, watching that it flows in easily by gravity, and being constantly on the alert for any change in the pulse, respiration or subjective symptoms." (*Neal*).

After operation the site of the puncture should be kept ***dry.***

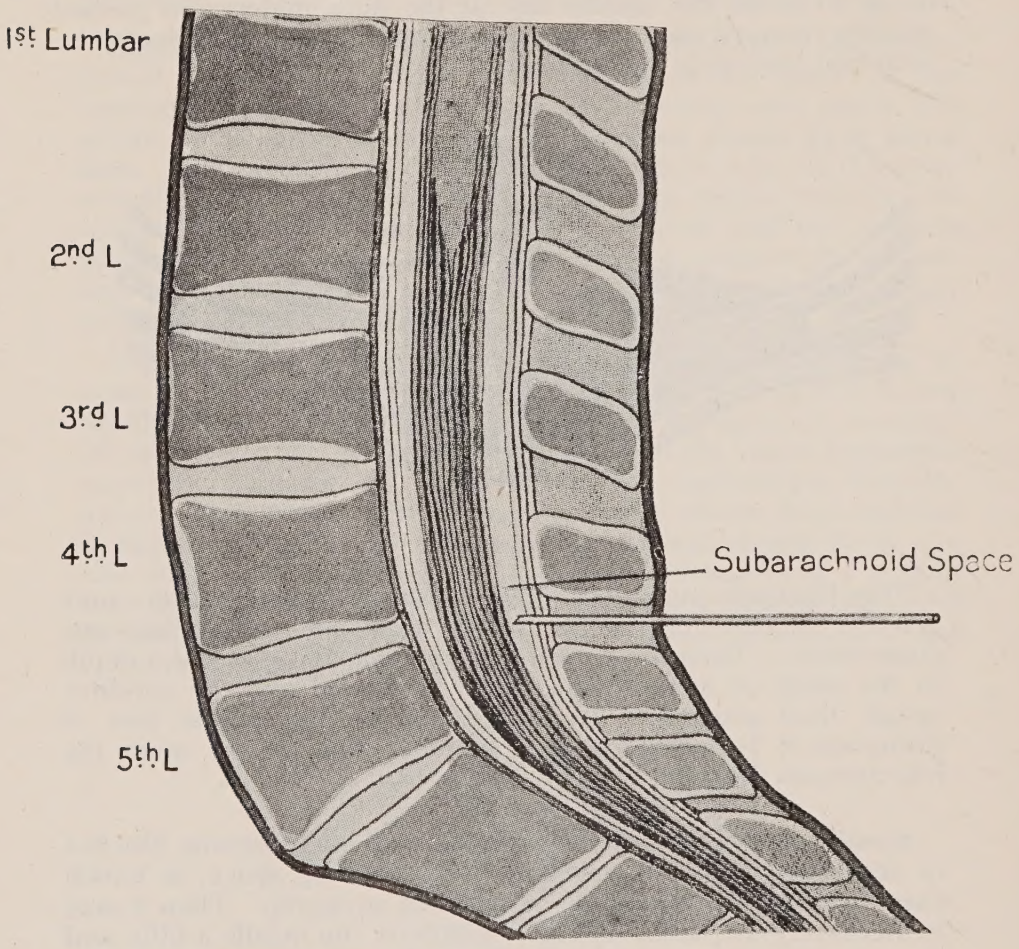

FIG. 3

The withdrawal of cerebro-spinal fluid and the injection of serum may be accompanied by various disturbances.

I. Headache—

(*a*) When the cerebro-spinal fluid is flowing out, this may become very severe before the final amount of fluid has been withdrawn. The flow should be interrupted so that the diminution of intracranial pressure may not be too rapid. If when this is done the headache does not quickly ameliorate it is a sign that withdrawal of fluid should be stopped. Morphia gr. $\frac{1}{6}$ given previously may prevent this trouble.

(*b*) When the serum is flowing in, may usually be relieved by lowering and extending the patient's head.

II. Pain in various situations—

(*a*) If a nerve be pricked during the performance of the puncture severe pain may be felt in the legs.

(*b*) The first few drops of serum especially in repeated injections may cause great pain in the legs or back, or even in more distant spots. This pain usually passes off when a few more cubic centimetres of serum have been run in. If this is not the case then the flow should be interrupted and resumed when the pains cease.

III. Disturbances of Respiration, etc.—

When in an adult some 20 c.c. of serum have been run in, then strained attention should be given to the pulse and respiration so as to appreciate the first signs of approaching trouble. Diminution in volume or slowing of the pulse or respiration are indications to stop the injection. The respiration, before stopping, usually slows and deepens and seems somewhat gasping, but it should not be allowed to reach this stage as it is soon followed by dilatation of the pupils, relaxation of the sphincters and collapse. Fortunately such serious symptoms are of infrequent occurrence. They are due to increased intracranial pressure and therefore fluid should at once be allowed to flow out of the canal, artificial respiration should be carried out and stimulants given. Certain experiments on animals suggest that atropin given intramuscularly might prove useful in such circumstances.

Sophian (1911), after an experience of some 1,500 lumbar punctures, strongly advises that blood-pressure readings should be taken during the operation. He considers that by this means the disturbances of respiration, etc., may be avoided. A drop of 10 m.m. of mercury while the cerebro-spinal fluid is flowing out is an indication to stop the flow, and a further drop of 10 m.m. while the serum is passing in limits the amount of serum which should be injected.

IV. In a considerable percentage of cases the administration of serum intraspinally is followed by a reaction, which begins in from 2-8 hours and continues for 8 hours or more as a rule. There is a rise of temperature, increased headache and restlessness.
"It may be questioned whether it is well to do lumbar puncture and give more serum before this reaction has passed off." (*Neal*).

The amount of preservative in the serum is not likely to have any bad effect when it is given intraspinally.

Intravenous Administration : In recent years it has been suggested that the intraspinal administration of anti-meningococcus serum should be reinforced by serum given intravenously. Herrick (1918) claims that cerebro-spinal meningitis is in most instances a primary meningococcus septicæmia ; that in at least 50 per cent. of the cases the diagnosis can be made in the premeningitic stage of sepsis ; and he advises that large doses of anti-meningococcus serum should be given intravenously. His results in 265 cases were :—

	No. of cases.	Mortality.
Treated by serum intraspinally alone or in conjunction with *small* doses of serum intravenously	137	34·3%
Treated with *small* doses of serum *intraspinally* and *massive* doses *intravenously*	128	14·8%

Other advocates of a similar course of treatment are Bloch and Hébert (1918), Bæslack, Bunce et al. (1918), Haden (1920), Kjær (1921). Neal (1916-1919) considers that serum should be given intravenously in cases showing marked evidences of sepsis, *e.g.*, the presence of a well-marked eruption.

It would appear advisable to give serum intravenously in cases of the fulminating type as these are often septicæmic.

Joint Troubles : In some cases there occurs an arthritis due to the meningococcus. The injection into the joint of anti-meningococcus serum has had an influence in arresting the progress of these inflammations.

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Description of apparatus suitable for the intraspinal administration of Anti-meningococcus Serum by the gravity method : This consists of a nickel needle containing a stylet, attachable by a metal mount to a suitable length of rubber tubing in which is inserted a glass window ; a funnel containing a plug of sterile wool for attaching to the upper end of the serum flask (air filter), also a clip for stopping the flow of serum. The apparatus fitted up for use is shown in fig. 4.

Directions for Use.

1.—If not already sterile, sterilise the needle, the rubber tube, the spring clip, and air filter, by boiling; plug the air filter with dry sterile wool.

2.—Immerse the capsule containing serum in warm sterile water at 40° C. or 104° F.

3.—Open the serum capsule at one end by means of a file.

4.—Join the end A of the sterile rubber tubing to the opened end of the capsule, clip the rubber tubing close to end B, and allow the capsule and tubing to remain in the sterile warm water till required.

5.—Perform lumbar puncture.

6.—Allow cerebro-spinal fluid to flow into a sterile receptacle preferably graduated.

7.—Remove serum capsule and clipped tube from the warm water, and open the other end of capsule with file. Attach the air filter C.

8.—Holding the capsule slightly higher than the end B of tube, cautiously open the clip till all the air is expelled and the tube is full of serum, then reapply clip.

9.—Affix end B of tube to the needle.

10.—Allow the serum slowly to enter the spinal canal by opening the clip, the serum capsule being held at first 2 or 3 inches above the site of puncture and gradually raised till the flow is seen to be slowly taking place.

11.—***After the operation the site of the puncture should be kept dry.***

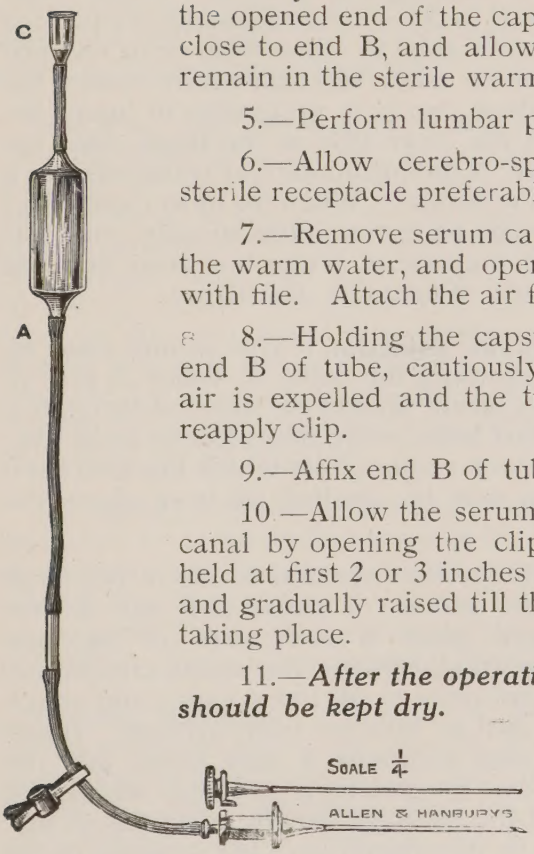

FIG. 4

Anti-Dysentery Serum (Multivalent) for the treatment of Bacillary Dysentery.

Anti-Dysentery Serum consists of the serum of horses which have been highly immunised against the *Bacillus dysenteriæ*, of which there are two main types—*B. dysenteriæ Shiga and B. dysenteriæ Flexner*. A large number of strains, particularly of the Flexner type, from widely scattered sources are used in the preparation of the Lister Institute Serum, which being thus multivalent, may be safely used whether the causal agent of the disease is a bacillus of the Shiga or of the Flexner type.

While much of the endemic dysentery which prevails in tropical and sub-tropical lands is caused by pathogenic amœbæ, epidemic dysentery due to the *B. dysenteriæ* occurs all over the world and this bacillus is also found in asylum or institutional dysentery, in some sporadic cases of ulcerative colitis and in certain forms of summer diarrhœa.

Method of Use : The syringe and needle should be boiled for five minutes immediately before the inoculation. The serum should be warmed to body heat. Before the injection is made the skin must be first well washed with soap and warm water and then with carbolic acid (1 in 20) or other antiseptic, or painted with a 2 per cent. solution of iodine in chloroform or in rectified spirit. The injection may be made subcutaneously, under the skin of the abdomen or flank, but it is preferable to inject the serum intramuscularly on the outer side of the thigh (into the body of the *vastus externus*) as the intramuscular route ensures a more rapid absorption of the serum. When the most rapid effect is required the serum should be given intravenously, and this method is recommended if the case is, when first seen, at a late stage and presents symptoms of toxæmia or collapse.

Technique of Intravenous Injection : The serum must be warmed to blood heat by standing the bottle in water at 110° F. If a deposit is present the serum should be strained through a piece of linen which has just been boiled (the piece of linen may conveniently be stretched over a wine-glass which has also been boiled) or the clear serum may be pipetted off from above the deposit.

The most convenient site for the injection is one of the large veins at the bend of the elbow. Cleanse the site as for subcutaneous injection and place a few turns of bandage sufficiently tightly round the arm to obstruct the venous circulation. Draw up the serum so as not quite to fill the syringe, and attach a sharp needle. Remove any air bubbles from syringe. Insert the needle into the vein and withdraw a little blood into the syringe so as to be sure that the needle is properly within the vein, and having removed the bandage slowly inject the serum. If a larger quantity has to be introduced than the capacity of the syringe permits, disconnect the syringe leaving the needle in the vein, and place the finger gently upon the vein whilst an assistant refills the barrel of the syringe. The serum may also be given by the gravity method.

In view of the possible occurrence of anaphylactic symptoms after the introduction of serum directly into the circulation it is a good plan to administer it largely diluted with saline, 200-400 c.c., by means of a funnel and flexible rubber tube. The saline itself is useful in severe cases of dysentery to replace the fluid lost from the tissues by the frequent evacuations. One minute should be taken to introduce the first few (5-10) cubic centimetres, and the patient's condition during the injection should be very closely watched. Should no untoward symptoms

manifest themselves the rest of the diluted serum may then be run in more rapidly. In very toxic cases the substitution for normal saline of a solution of glucose, 5·5 per cent., in distilled water was found valuable by Graham (*Lancet*, 1918, Jan. 12, p. 51).

Whichever method of administration is used, every precaution should be taken to prevent infection occurring from the skin of the patient, from the instruments or from the hands of the operator.

Dosage : *Prophylactic.* Anti-Dysentery Serum may be used as a prophylactic when an epidemic is in progress but the immunity conferred lasts only a few weeks. An appropriate dose is 20 c.c. given subcutaneously in the flank or abdomen.

Curative. The amount of serum administered will depend upon the severity of the case, and upon the interval between the onset of the illness and the commencement of treatment. An initial dose of 40-60 c.c. given intramuscularly is suggested for a case of moderate severity seen at an early stage : this dose should be repeated daily till improvement sets in. In grave cases 60-100 c.c. should be given and repeated daily if necessary. Graham (*loc. cit.*) from an experience of over 500 cases in the British Salonika Force is of opinion that the best results are obtained by intravenous injections of 60-80 c.c. of serum with 150-300 c.c. of normal saline twice daily for the first two days and once daily for the next two.

The effect of the serum is manifested by the relief of pain and tenesmus, by a rapid diminution in the number of stools, by a fall of temperature and by a great improvement in the general condition of the patient. Joint pains and rashes of various types accompanied by a rise in temperature sometimes occur after the injection. These need cause no apprehension.

General Remarks : The value of Anti-Dysentery Serum was amply demonstrated in the late war, and it is not an exaggeration to say that as a serotherapeutic agent it ranks next to diphtheria antitoxin. *But experience has shown that, like diphtheria antitoxin and tetanus antitoxin, this serum must be administered as early as possible if the maximum therapeutic effects are to be secured.*

In assessing the efficacy of the serum in any particular case or series of cases, it is essential to take into account and to record the time of administration in relation to the onset of the disease. The value of reports on the utility of serum treatment is much reduced if this information is omitted. *Early diagnosis is of the very utmost importance in the serum treatment of dysentery.*

Since this serum is without effect in cases of pure amœbic dysentery, the type of infection, whether bacillary or amœbic, should be determined without delay. As soon as the patient is found to be passing dysenteric stools, a perfectly fresh specimen of the blood and mucus should be examined for the presence of

motile amœbæ possessing the features of *Entamœba histolytica*, particularly the inclusion of red blood corpuscles. If pathogenic amœbæ are not found, and if a stained film of the blood and mucus reveals an abundance of polymorphonuclear leucocytes—a constant and characteristic sign of bacillary dysentery— there should be no hesitation in treating with serum, for the isolation of the dysentery bacillus from the stools, even of typical cases of bacillary dysentery, is not always successful and the chances of successful isolation of the bacillus diminish progressively with the duration of the illness.

J. Anderson (*Lancet*, Nov. 12, 1921, p. 998) describes the salient features of the cytology of the stools as follows :—

Bacillary Dysentery—

(1) A preponderance of polymorphonuclear leucocytes which constitute on an average 90 per cent. of the cellular exudate.
(2) Eosinophile cells seldom or never present.
(3) Macrophages present in limited number—averaging about two per cent.
(4) Absence of "Pyknotic" bodies.

Amœbic Dysentery—

(1) A small proportion of polymorphonuclear leucocytes—averaging only 7½ per cent.
(2) Presence of eosinophiles is a conspicuous feature—average 2-5 per cent.
(3) Macrophages not found.
(4) "Pyknotic" cell remnants present—average 83 per cent.

Serum should be given without waiting for the result of a bacteriological examination, and its administration should be continued on clinical grounds alone in spite of negative bacteriological reports. It is well to bear in mind that the responsibility for the diagnosis of dysentery devolves primarily, not upon the bacteriologist, but upon the physician, *who should never omit to examine personally the stools* of the patient for the presence of blood and mucus as soon as the symptoms suggest the possibility of a dysenteric infection.

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Fletcher, Wm. and Jepps, Margaret W., *Dysentery in the Federated Malay States* (London, 1924).
Haughwout, F. G., *Journal Amer. Med. Assn.*, 1924, vol. 83, p. 1156 (11th October).

Anti-Plague Serum.

This preparation consists of the serum of horses which have been immunised against the plague bacillus, and to it is added not more than 0·35% cresylic acid as a preservative.

It is used both as a therapeutic and a prophylactic agent.

Therapeutically Anti-Plague serum is, unfortunately, not very potent and, as the disease runs a rapid course, it is necessary to press the treatment.

For prophylactic use the serum is useful during an epidemic, or in the case of individuals who have been exposed to infection and may have already become infected. The duration of the immunity produced is very brief, probably not more than twelve days.

Dosage : At the earliest moment after the disease has declared itself, 50 c.c. should be injected intravenously and 50-100 c.c. intramuscularly or subcutaneously. In 12-24 hours these amounts should be repeated. For a prophylactic dose 20 c.c. should be injected subcutaneously.

The syringe and needle should be boiled for five minutes immediately before the inoculation.

Subcutaneous Injection : The injection is usually made under the skin of the abdomen or flank, and a swelling appears, which is, however, absorbed in a few hours. A little tenderness sometimes persists for twenty-four hours. The skin must be first well washed with soap and warm water, and then with carbolic acid (1 in 20) or other antiseptic before the inoculation is made or painted with a 2% solution of iodine in chloroform or in rectified spirit. When the needle has been withdrawn the site of the puncture should be protected against infection.

Intramuscular Injection—see page 6.

Intravenous Injection—For Technique see p. 6.

Joint pains and rashes of various types, accompanied by rise in temperature sometimes occur after the injection. These need cause no apprehension.

*NOTE.—Before giving an intravenous injection of serum it is always advisable to make enquiry as to previous injections of serum and whether the patient has any idiosyncrasy (such as liability to attacks of asthma, to be affected by emanations from horses, etc., because the risk of an anaphylactic trouble occurring is distinctly greater after intravenous than after intramuscular or subcutaneous injection.

Anti-Pneumococcus Serum.

This preparation consists of the serum of horses which have been immunised against the Pneumococcus. It contains not more than 0·35% of cresylic acid as a preservative.

A definite opinion cannot be expressed with regard to the therapeutic value of Anti-Pneumococcus Serum, but beneficial results are reported to have followed its administration, especially in cases due to infection by organisms of the Type 1 group of pneumococci A good result is more certain if the treatment be

started before the onset of a bacteræmia. Serum should, therefore, be given as early as possible in the attack, so as to exercise its effect before there has been any invasion of the blood by the pneumococcus.

Directions for Use : When using serum every precaution should be taken to prevent infection from the skin of the patient, from the instruments or from the hands of the operator. Nor should it be forgotten that some individuals are hypersensitive to horse serum.

Serum should always be warmed to body heat before injection.

The syringe and needle should be boiled for five minutes immediately before use. Before the injection the skin must be well washed with soap and warm water, and then with carbolic acid (1 in 20) or other disinfectant, or painted with a 2% solution of iodine in chloroform or in rectified spirit.

Dosage : Some clinicians strongly urge the importance of administering large doses (*e.g.*, 50 c.c.—100 c.c.) intravenously every eight hours until the symptoms ameliorate ; others, on the contrary, report beneficial results from 20 c.c.—40 c.c. subcutaneously every day. The decision as to the dosage ultimately rests with the physician in charge of the case, and if he wishes to steer a middle course he might give 50 c.c. intramuscularly and repeat it as occasion requires.

Erythematous and other rashes, and joint pains, may sometimes appear from four days to five or six weeks after the injection. These need cause no apprehension.

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R. Cole, Journl. Amer. Med. Assoc., 1921, 76, 111.
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B. Weill-Halle et al. Bull. Soc. Med. des Hopitaux Paris, 1922, 46, 227.
E. E. Glynn and L. Digby, Special Report Series No. 79, Medical Research Council.

Anti-Scorpion Serum. For the treatment of Scorpion Stings.

This preparation consists of the serum of horses which have been immunised against the venoms of the Egyptian scorpions :

1. *Buthus quinque striatus.*
2. *Prionurus citrinus.*
3. *Buthus maurus.*

It contains 0·5 per cent. of carbolic acid as a preservative.

The serum should be kept in a dark, cold place (preferably in an ice safe). If kept thus it will remain potent for at least a year.

Dosage : The dose is 1 phial.

Site of Injection : The injection should be made directly into the site of the sting. If the sting is in a finger or other position where it is not possible to inject the whole dose, as much as can be conveniently introduced without causing pain should be

injected into the site of the sting, and the remainder of the dose into some convenient region higher up the limb. It is of the *greatest importance* that the injection should be made as soon as possible after the sting.

Normal Horse Serum.

Normal Horse Serum has been applied locally to old wounds and chronic ulcers with success, apparently owing to the anti-tryptic substance contained in the serum inhibiting the destruction of the newly-formed epithelium by the proteolytic ferments in pus.

After-effects of Serum Injection.

Rashes.

Although rashes may occur in diphtheria and other toxic and septic diseases where no antitoxin has been used, there is no doubt that the serum treatment is itself the cause of a large number of rashes. The production of a rash is not due to anything connected with the immunisation, or to the antibodies in the serum, but is due to something inherent in the serum of the horse, as the injection of serum from a normal, healthy horse may be followed by rashes. Every individual is not equally susceptible to these after-effects, for the same batch of serum may cause trouble in one patient and not in another. These rashes may be accompanied by a slight rise of temperature. Beyond this, and the nervous irritation produced by their presence, no bad after-effects ensue.

In order to prevent or minimise these after-effects of serum injection, the use of calcium chloride or lactate has been recommended. A dose of 20 grains may be given on the day of the injection and on the two following days.

The commonest forms of these rashes are urticarial, erythematous and scarlatiniform eruptions.

They may occur from four days to five or six weeks after the injection, but most frequently from the eighth to the fourteenth day.

Arthropathies.

Joint-pains, which may affect one or more joints, accompanied in certain cases by stiffness, slight swelling and neuralgia, are much rarer after-effects than the skin eruptions. They occur usually about the same time as these, and like them are due to something inherent in the serum of particular horses. This condition of the joint never goes on to suppuration. As a rule it disappears in a few days, though more rarely it may persist for a few weeks.

The Diphtheria Antitoxin, Tetanus Antitoxin, Scarlet Fever Antitoxin, Anti-Dysentery Serum and Anti-Scorpion Serum sent out by the Lister Institute are refined, the object of the refining process being to remove as much as possible of the non-therapeutic proteins of the serum.

The "Schick Test" and Active Immunisation against Diphtheria.

Historical Notes : It is a matter of common knowledge and observation that during an epidemic of disease some individuals are struck down while others escape. Why this is so is a question which has puzzled men's brains for ages. It is only since the discovery of diphtheria toxin and antitoxin that we have got an inkling of an answer, and even now it cannot be said that a complete solution of the problem has been found. It was first noticed that among horses used for the production of diphtheria antitoxin some were more susceptible than others to the toxin of the diphtheria bacillus. Then it was discovered that in the blood of some of the animals prior to immunisation small quantities of diphtheria antitoxin were present, and a little later antitoxin was also demonstrated in the blood of human beings.

Since the discovery of diphtheria toxin and antitoxin it has been known that, when injected beneath the skin in appropriate quantity, the toxin would cause necrosis of the skin at the site of injection, and that the destruction of the skin could be prevented by the administration of antitoxin in appropriate amount. Basing his studies on these facts, Römer (1909) worked out a method of measuring very small amounts of diphtheria antitoxin. He found that by injecting varying minute quantities of diphtheria toxin, *not beneath* but *into the substance* of the skin, he could, with a certain dose, produce merely redness, and with a somewhat larger dose a slight local necrosis (scaling) of the superficial layers of the skin, and that this toxic effect could be completely neutralized by antitoxin either given with the toxin or injected previously. Choosing this necrosis-producing dose he devised a method by which minute amounts of diphtheria antitoxin can be estimated *without causing any injury to the experimental animals* other than slight local necrosis. If antitoxin injected previously into an animal can neutralize this necrogenic dose it follows that antitoxin already present in the blood of an animal should also effect neutralization. This was found to be the case.

About the same time, Schick (1908), following the lead given by Professor v. Pirquet in the case of tuberculosis, studied the action of diphtheria toxin on the skin when applied to a scarified area. He was unsuccessful until he used toxin which had been concentrated ten times. With this strong toxin he obtained a specific reaction which, as it occurred in normal persons, could not be used for diagnostic purposes, but by means of which he thought we might arrive at an exact and rational dosage of antitoxin. He concluded that a positive cutaneous reaction was a measure of the individual susceptibility to diphtheria, but he did not at that time suggest it as a means of separating the

immunes from the non-immunes, though he thought that failure to obtain a cutaneous reaction might be explained by Wassermann's observation of the presence of small quantities of diphtheria antitoxin in the blood of some human beings. Further studies, in collaboration with Novotny (1910), confirmed this view and led them to think that the intracutaneous injection of very small doses of diphtheria toxin according to Römer's method might be more convenient for future studies. Later (1913) he showed that Römer's observations might be applied to man, and suggested injecting a very small amount of diphtheria toxin *into the skin* of human beings to separate those who did not possess antitoxin in their blood from those who did, on the assumption that the latter would be less likely to contract diphtheria if exposed to infection. In other words, he proposed, by the use of the "Schick test" to divide the immune from the non-immune members of the population. The former, he believed, could be left to take care of themselves while prophylactic attention was concentrated on the latter.

Prophylaxis can be carried out in two ways :—

1. During exposure to infection, by the injection of diphtheria antitoxin to produce a temporary *passive* immunity.
2. At other times by the injection of a mixture of toxin and antitoxin to produce *active* immunity.

The idea of producing an active immunity in the human subject to diphtheria toxin dates back many years. For instance, Dzsierzgowski (1902) gave himself injections of diphtheria toxin and demonstrated antitoxin in his blood. Bandi and Gagnoni (1906) found that the injection of an extract of the diphtheria bacillus either alone or combined with antitoxin caused the appearance of antitoxin in the blood of the subjects tested. Bingel (1909) used diphtheria toxin intracutaneously with a similar result. In 1907 and 1909 Theobald Smith showed that after the subcutaneous injection in guinea pigs of mixtures of diphtheria toxin and antitoxin which produce no local lesion recognisable during life, no general disturbance indicated by loss of weight and no paralysis, the acquired immunity remains in evidence at least two years. He further suggested that, proceeding along these lines, it would be possible to work out a *harmless, easily controlled and practical method for the active immunisation of the human subject*, and he pointed out that it would be applicable only as a general protective measure and not serviceable against an immediate danger, since active immunisation takes several weeks to develop.

V. Behring appears to have been the first to carry out this method of production of active immunity in human beings. The description of the method of preparing his mixture is too vague to be followed, and it is to Park, Zingher, and their co-workers that we are indebted for the development of a method which fulfils the conditions laid down by Theobald Smith, and which, if generally adopted, would eradicate diphtheria even as smallpox has been stamped out by vaccination.

The Schick Test.

The "Schick test" was proposed by Professor Schick in 1913 with the idea of separating those who are susceptible to an attack of diphtheria from those who are not. Since then its value has been established in Europe and America. It consists of the injection *into the substance* of the skin, *not beneath it*, of a very small quantity of diphtheria toxin. The value of the test depends entirely upon observing certain precautions both in carrying it out and in reading the results.

The toxin must be a reliable stable toxin. The dose injected should be 1/50th or 1/40th of the minimum lethal dose for a guinea pig of 250 grammes weight, and this quantity should be contained in not more than 0·2 c.cm. of the solution. On account of the possibility of the occurrence of what is called a "pseudo reaction" it is necessary to make simultaneously a control injection of a similar quantity of heated toxin.

The best place for the injection is at the wide part of the flexor surface of the forearm a short distance below the bend of the elbow, and to prevent mistakes it is usual to make the *control* injection into the *left* arm and the *toxin* into the *right* arm. The needle should be very fine, 1/4—3/8 inch in length, and should have a short sharply bevelled point so that when the needle is inserted *into the skin* with the bevel towards the surface the point may be quickly covered. Care should be taken to insert the needle for 1/8—3/16 inch parallel with the surface of the skin and just below the epidermis, when, *if in the substance of the skin*, it will be found that a distinct amount of force is required to make the injection. If properly performed the immediate result of the injection is the appearance of a circumscribed roundish white elevation dotted over with little pits (the opening of the hair follicles). The little swelling does not disappear at once, but may take half-an-hour to subside.

Every care should be taken to prevent infection from the skin of the patient, from the instruments, or from the hands of the operator.

The results which follow the intra-cutaneous injection may be of several kinds.

Negative Reaction : There is no change in the skin except the very slight and transient redness due to trauma. Persons giving a *negative* reaction are *immune* to diphtheria.

Positive Reaction : At the end of 24 hours there is seen at the site of injection a slightly infiltrated circumscribed patch of redness varying in diameter from 10 to 30 m.m. This gradually becomes more marked and reaches its height about the fourth day. It persists for several days, gradually fading away with a varying degree of desquamation, and leaves a slight brownish pigmentation. Occasionally the appearance of the reaction is delayed for a day or two. Persons giving a *positive* reaction are *liable to contract* diphtheria when exposed to infection.

Pseudo Reaction: This is not a true toxin reaction but resembles the *positive* Schick reaction. That it is not due to diphtheria toxin is proved by its occurrence following the injection of solutions of diphtheria toxin in which the toxin has been destroyed by heat.

The suggested explanation of this reaction is that some persons, and particularly those who have had an infection with the diphtheria bacillus, are susceptible to *some substances, other than the toxin*, present in a diphtheria culture.

The pseudo reaction is differentiated from a positive reaction in that the redness is usually brighter, the reaction reaches its maximum earlier (on the first or second day) and passes off more rapidly, leaving very slight pigmentation and usually no scaling. It is observed to be fading on the fourth day, when the *positive* reaction is at its height. Occasionally, however, the pseudo reaction is more marked than usual and persists for several days beyond the usual time.

To be able to recognise the pseudo-reaction is of great importance because otherwise a person would be judged susceptible when in reality he was immune. It is to obviate this source of error that it is necessary always to make the control injection of the same amount of diphtheria toxin which has been heated at 75° C. for ten minutes. In the case of a *pure* pseudo reaction the appearance of both arms is the same ; the reactions reach their maximum intensity together, and pass away at the same time. Persons giving a *pure pseudo* reaction are *immune* to diphtheria.

Positive Reaction + Pseudo Reaction: In this case, to the positive reaction is superadded a pseudo reaction. The distinguishing points are that the reaction at the site of the *control* injection attains its maximum and subsides more quickly than that at the site of the *toxin* injection.

Persons giving this *combined reaction* are *susceptible* to diphtheria, and are liable to react energetically when injected with toxin-antitoxin mixture for the purpose of producing active immunity.

Note: ***It is advisable to examine the sites of injection daily until the fifth day, and to keep the patient under observation for ten days. The second and fourth days are the critical days, and an examination of the arms on these days should on no account be omitted.***

B. Schick (1913). *Münch. Medz. Wochensch*, p. 2608.
A. Zingher (1921). *Jour. Amer. Med. Assoc.*, vol. 77, p. 835.
T. E. Dickinson (1922). *Lancet, I*, 312.

Diphtheria Toxin-Antitoxin Mixture

(For active immunisation only).

This preparation consists of a mixture of diphtheria toxin and diphtheria antitoxin.

It is employed for the purpose of producing an active immunity to diphtheria in those who, by means of the Schick test, have been shown to be susceptible to this disease.

According to Zingher (1921) the large majority of children between the ages of six months and five years give a *positive* Schick reaction, and therefore the omission of this test in this age group is not of much consequence, and all these children should be injected with toxin-antitoxin mixture. Above the age of five years only those who give a *positive* Schick reaction should receive prophylactic inoculations.

Site of Injection : The upper arm in the neighbourhood of the insertion of the deltoid muscle is the site usually chosen, but as the reaction is likely to be increased owing to the arm not being kept at rest after the injection, it may be thought preferable to choose some other convenient situation, *e.g.*, the flank.

Every precaution must be taken to prevent infection from the skin of the patient, from the instruments, or from the hands of the operator.

Dosage : 1 c.cm. given *subcutaneously* at intervals of a week for three doses. For children of 12 months and under, 0.5 c.cm. given at similar intervals. Though, from experience both in America and Germany, it appears that very young children are more tolerant than older children and adults of the toxin-antitoxin mixture, yet, as the reaction which follows the injection is occasionally somewhat marked, it may be considered preferable to begin with a smaller dose, say 0.2 c.cm., and to follow it up with doses of 0.4 c.cm., 0.8 c.cm. and 1.5 c.cm., at intervals of 5-7 days. Such a procedure is especially necessary in the case of those who give a *positive+pseudo reaction.*

As evidence of the harmlessness of the injections of toxin-antitoxin mixture the experience of Zingher (1921) may be quoted : "In over 50,000 injections of toxin-antitoxin mixture which have been given during the past four months, we have not seen a single serious result or a single infection. This statement must be emphasised as the swelling of the arm at the site of injection leads some parents to think that the child has 'blood poisoning.'"

The active immunity resulting from the injections of the toxin-antitoxin mixture takes some weeks to develop, and all subjects do not respond in the same degree. In one series of the non-immune children to whom Zingher had given immunising injections of toxin-antitoxin mixture, 148 or 87.5% were found to be immune when tested five months later by the Schick test.

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A. Zingher (1921). Jnl. Amer. Med. Assn. Vol. 77 p. 835

Bacterial Vaccines.

Bacterial vaccines as prepared by the Lister Institute are emulsions of killed bacteria in physiological salt solution standardised to contain a certain number of micro-organisms per cubic centimetre. They are prepared by growing the specific organism, or organisms, in suitable media, the resultant growth from which is sterilised by heat or the addition of an antiseptic.

Prophylactic Use.—In the case of bacterial vaccines it is usually advisable to give an inoculation every week or ten days. The dose should be doubled each time unless the local or general reaction is so marked as to indicate the necessity of repeating or even diminishing it before gradually proceeding to higher doses again. Alternatively the interval between inoculations may be increased.

Therapeutic Use.—In acute infections the dosage of vaccines should be in inverse proportion to the acuteness of the infection. In more chronic infections, such as tedious septic processes and the like, the initial dosage may be on a considerably higher scale.

For *children,* the dosage should be diminished by giving from a tenth to a half of an adult dose according as the age varies from that of infancy to that of early puberty.

Vaccines should be well shaken to secure a homogeneous emulsion.

Inoculation is usually made subcutaneously. The most convenient sites for the injection are the arm about the deltoid insertion and the sub-clavicular region, on the left side in right-handed persons, the skin being sterilised by painting with 2 per cent. iodine solution and the proximity of superficial veins avoided.

The syringe should be well boiled before use. The phials are opened easily by snapping the neck after a nick has been made in the glass with a small file.

To withdraw vaccine from a rubber-capped bottle *do not remove the cap.* Place a drop of Lysol on the cap, plunge the needle of a sterilised syringe through the rubber, invert the bottle, and draw the syringe piston till the required quantity of vaccine is drawn into the barrel. The puncture in the rubber cap will close up when the needle is withdrawn.

Vaccines employed solely as Prophylactics against Plague, Typhoid and Paratyphoid Fevers and Cholera.

Plague Vaccine.

Plague Vaccine consists of a killed culture of the *B. pestis* to which 0·5 per cent. carbolic acid has been added, and is standardised to contain approximately 3,000 million bacilli per cubic centimetre.

The immunity conferred by this material is not established for several days after the injection, but is of a more lasting character than that obtained by the use of Anti-plague Serum.

Persons exposed to infection should be inoculated every six months.

Dosage: When opportunity allows of only a single injection the dose should be: For adults, 1 c.c.; for children over 10 years of age, ½ c.c.; under 10 years, ¼ c.c. A better immunity is obtained by giving two doses, *e.g.:* For adults, ½ c.c. and 1 c.c. with an interval of 8-10 days between them.

The injection may be followed by local swelling and redness, and by enlargement of the neighbouring lymphatic glands. These local symptoms may be accompanied by headache, rise of temperature, sickness and general malaise, which usually passes off in 24-48 hours. It is to be noted that the susceptibility of different individuals varies very much. A dose which causes no reaction whatever in one person, may give rise to headache, etc., in another.

Typhoid and Paratyphoid Vaccine.

This vaccine commonly called the T.A.B. vaccine has taken the place of the old Typhoid vaccine, the value of which as a prophylactic against Typhoid fever has been firmly established. As there is no evidence, however, that the simple Typhoid vaccine affords protection against the Paratyphoid fevers (Paratyphoid A. and Paratyphoid B.) which likewise are liable to occur in circumstances favourable to the propagation of Typhoid fever, it was during the latter years of the late war the practice to combine in one vaccine the protective agents against both Typhoid and Paratyphoid fevers. The inoculation with this vaccine of nursing staffs in fever hospitals, persons proceeding to infected areas anywhere, or to the tropics, is strongly recommended. If complete double inoculation is carried out, the immunity is regarded as lasting about twelve months, at the end of which it is advisable to maintain the immunity by a further dose of 1 c.c. of the preparation.

Dosage: For the primary inoculation a dose of ½ c.c. containing 500 millions of *B. typhosus*, and 375 millions each of *B. paratyphosus A.* and *B. paratyphosus B.* should be given and for the second dose, 7-10 days later, double the above number. The inoculation is followed after three or four hours by some pain and tenderness at the site of injection and occasionally by fever and general malaise. All these symptoms have usually disappeared by the third day. Rest and abstention from alcohol after the inoculation are recommended as tending to alleviate these symptoms. The second dose is usually followed by much less local reaction and the constitutional symptoms are generally absent.

Typhoid Vaccine may be had separately if desired, but the employment of the T.A.B. vaccine alone will be found the most convenient method of securing protection against the enteric group of fevers.

Therapeutic Use of Typhoid Vaccine.

Opinions are divided as to the value of Typhoid vaccine used therapeutically and as to the dosage to be employed. Generally about 300 millions given every four or five days is recommended. (See *Proceedings Roy. Soc. Med.*, 1910, I., p. 82, and *Lancet*, 1914, I., p. 312.)

Cholera Vaccine (Multivalent).

This vaccine consists of an emulsion of cholera vibrios, killed by the addition of 0·5 per cent. of pure carbolic acid. It is employed as a prophylactic agent against Asiatic cholera.

The protection afforded by this vaccine probably does not last longer than 4—6 months.

Dosage: An initial dose of ½ c.c. containing 5,000 million organisms should be injected. The injection is followed by slight local reddening and swelling, together with a rise of temperature and some malaise. These symptoms subside in one or two days. A second dose of 10,000 million organisms should be administered after 7-10 days.

Typhoid, Paratyphoid and Cholera Vaccine.

This vaccine is of service where a journey is contemplated to countries in which enteric disease and cholera are known to be endemic, and where it is of some importance to secure immunity in a limited time and without multiple injections. It consists of an emulsion of killed Typhoid, Paratyphoid and Cholera organisms and is standardised to contain, in each one cubic centimetre, 1,000 million *B. typhosus*, 750 million each of *B. paratyphosus A. and B.* and 10,000 million *V. choleræ.*

Dosage: For the first dose half of a cubic centimetre should be given followed by one cubic centimetre, a week or ten days later.

A reaction similar to that of T.A.B. is generally obtained when this vaccine is used.

Vaccines in General Use for Therapeutic and Prophylactic Purposes.

Acne Vaccine.

It has been claimed that in certain cases of Acne where the ordinary staphylococcic vaccines have failed to ameliorate the condition, good results are obtained by the use of a mixed vaccine of the Acne Bacillus (Sabouraud) and the *Staphylococcus aureus.*

Dosage: The initial dose is usually 125 million Staphylococci and 125 million Acne Bacilli. This dose may be increased to 250 and 500 millions of each organism, with the usual interval of 7-10 days between successive doses.

Staphylococcus Vaccines.

For the Treatment of Acne, Furunculosis and Sycosis.

For this purpose different vaccines are employed—one prepared from a pure culture of *Staphylococcus aureus*, which is recommended for furunculosis and sycosis, and a second, prepared from a mixture of pure cultures of *Staphylococcus aureus*, *Staphylococcus citreus*, and *Staphylococcus albus*, which is recommended for acne. These vaccines consist of an emulsion of the killed staphylococci. As furunculosis and sycosis are not always due to *Staphylococcus aureus* it is most advisable that a bacteriological diagnosis of the pus from the furuncles or acne pustules be made, in order to determine which species of staphylococcus is responsible for the condition.

Dosage: For the first dose 500 million cocci should be injected. Subsequently the dose may be gradually increased to 2,000 million cocci. The usual interval of 7-10 days must always be allowed to elapse between the injections, the physician carefully watching the effect, and if too much reaction occurs around the furuncles and acne spots the dose must be diminished. These vaccines are put up in phials containing 500, 1,000 and 2,000 millions per c.c. respectively.

Gonococcus Vaccine.

This vaccine consists of an emulsion of killed gonococci, recently isolated from the body, and is employed in chronic local infections due to the gonococcus.

Dosage: Systems of dosage with this vaccine differ greatly, especially with regard to initial doses. The smaller doses of $2\frac{1}{2}$ and 5 millions may be repeated every 3-4 days, but if it is considered admissible to proceed to higher doses the intervals between them should be increased to 7-10 days. The vaccine is put up in phials containing 5, 10, 50, 100 and 300 millions.

Pneumococcus Vaccine (Multivalent).

This vaccine is employed in the treatment of localised pneumococcus infections and acute pneumonia. It is prepared from several strains of the pneumococcus isolated from cases of pneumococcal infection in man.

Dosage: For the first dose, 5 or 10 million cocci are recommended. Subsequently the dose may be increased to 20 millions or more. In pneumonia, should the temperature, which usually falls under such an inoculation, begin to rise again, a second or more doses can be given at intervals of 36 hours. Higher doses are often given. The vaccine is put up in phials containing 5, 10, 50 and 100 millions.

Streptococcus Vaccine (Multivalent).

This vaccine is prepared from several strains of the organism, derived from cases of erysipelas and other streptococcal infections in man. It is used for the treatment of localised streptococcus infections.

Dosage: For the first doses, 5 or 10 million cocci should be injected, and may be given every 4-5 days. Subsequently the dose may be increased to 20 millions and more, but an interval of 7-10 days should always elapse between the larger inoculations. The vaccine is put up in phials containing 5, 10, 20, 50 and 100 millions.

Streptococcus rheumaticus Vaccine.

This vaccine is prepared from Streptococci isolated from cases of acute rheumatism and from cases of rheumatoid arthritis. Some success has followed its use in rheumatoid arthritis and similar conditions.

Dosage: For the first dose 5 million cocci should be given. Subsequently the dose may be gradually increased to 200-400 millions. The early doses of 5 and 10 million may be given at intervals of 4-5 days; higher doses need intervals of 7-10 days. The vaccine is put up in phials containing 5, 10, 25, 50 and 100 millions per c.c.

Micrococcus catarrhalis Vaccine.

This vaccine is prepared from several strains of the *Micrococcus catarrhalis*, an organism frequently found in large numbers in the discharges in cases of acute or chronic catarrh of the respiratory passages. How far it is responsible for the catarrhal condition is still uncertain, but it is claimed that a vaccine prepared from it frequently does good. The vaccine is also used in cases of pyorrhœa alveolaris.

Dosage: The initial dose is 25 millions, to be followed at intervals of 7-10 days by further doses, rising gradually to 100 or 250 millions. The vaccine is put up in phials containing 25, 50, 100 and 250 millions.

Compound Catarrhal Vaccine.

Pure infections with one type of organism are not met with as frequently as mixed infections in catarrhal conditions of the respiratory passages. The organisms most often present are assumed to be the most common causes of acute catarrh, though absolute proof is not forthcoming. In addition to *B. influenzæ*,

Pneumococcus and *M. catarrhalis*, which are believed to be the most frequent primarily infecting organisms, *Streptococcus longus* and Staphylococcus appear to be responsible for many of the secondary infections. A mixed vaccine has been prepared from the above-mentioned five kinds of bacteria. This may be used as a prophylactic or in acute infections. In the latter case smaller doses should be used, and it is much more satisfactory to determine the prevailing type of organism present by bacteriological examination and to use a vaccine specially prepared.

Dosage : The first prophylactic dose is : 50 millions *B. influenzæ*, 10 millions Streptococcus, 25 millions *M. catarrhalis*, 25 millions Pneumococcus, 125 millions Staphylococcus. Subsequent doses should be given at intervals of 7-10 days, and the amount given raised gradually to eight times the original dose. After this maximum has been reached, prophylactic doses of four or eight times the initial dose may be given every four or five weeks. The vaccine is put up in phials containing 235, 470, 940 and 1880 millions per c.c. respectively.

Compound Influenza Vaccine.

The chief organisms found in the catarrhal secretions of the respiratory passages in cases of Epidemic Influenza are the *B. influenzæ*, the Pneumococcus and Streptococcus. A vaccine has been prepared containing these three types of bacteria. It is primarily intended for use as a prophylactic. It may also be used in treatment during an attack, but in this case its effect should be carefully watched and much smaller doses should be used, *e.g.*, 1/5th to 1/20th of the prophylactic doses should be given, the smaller being used in more severe cases.

For Prophylaxis : ADULTS—First dose containing 330 million organisms (200 million *B. influenzæ*, 100 millions Pneumococcus, 30 millions Streptococcus). Second dose containing double the quantities in first dose. The usual interval of 7-10 days should elapse between the doses. The vaccine is put up in phials containing 330 and 660 million organisms per c.c. respectively.

Bacillus septus Vaccine.

This organism is sometimes found in large numbers in catarrhs of the respiratory passages, frequently in association with other organisms ; but its relation to the pathological condition is still uncertain. Vaccines prepared from it are said to sometimes have a markedly beneficial action in acute catarrhs.

Dosage : The first dose is 100 millions. Subsequently the dose may be gradually increased at intervals of 7-10 days to 400 millions. The vaccine is put up in phials containing 100, 200 and 400 millions per c.c.

Pneumobacillus (Friedlaender) Vaccine.

This organism, which may occur in chronic abscesses and infections of the urinary tract, is frequently met with in coryza, in other catarrhal conditions of the respiratory tract, and sometimes in broncho-pneumonia, especially in children.

Dosage : The first dose is 50 millions. Subsequently the dose may be gradually increased at intervals of 7-10 days to 200 millions. The vaccine is put up in phials containing 50, 100 and 200 millions per c.c.

Coley's Fluid for Cancer and Sarcoma.

This fluid is prepared according to Dr. Coley's new method, and differs from the original Coley's Fluid. It contains the combined toxins of the streptococcus of erysipelas and of the *Bacillus prodigiosus*. Treatment is based on the observation that malignant growths may decrease in size, or even completely disappear after an attack of erysipelas. Its use is advocated in inoperable cases of malignant disease, especially sarcoma. The fluid is injected hypodermically in the tumour or elsewhere with aseptic precautions.

Dosage : At first it is necessary to use very small doses, that is, not more than one quarter of a minim, but the dose may be gradually increased till a rise of temperature to 102° to 104° F. is produced. Sterile distilled water should be employed in making the requisite dilutions. Doses are given either daily or every other day.

Anti-Variolous Vaccine

(CALF LYMPH).

Anti-Variolous vaccine, or vaccine proper, differs from other therapeutic agents of microbial origin in that it is a preparation containing a *living* micro-organism—the specific micro-organism of vaccinia or cow-pox (*vacca*, a cow, hence *vaccina*).

The prophylaxis of vaccination depends on immunity being conferred on the subject through inoculation of vaccine of sufficiently high potency. The subject thereby contracts vaccinia and is enabled to manufacture in his own tissues a substance antagonistic to the specific organism of variola.

Production of Vaccine : A young and healthy animal is selected and is kept in quarantine for a period to ensure its being in perfect health. An area of the animal's skin is shaved and rendered perfectly clean, and slight incisions are made on this prepared area into which highly potent vaccine is inoculated. On the fifth day after inoculation vesicles occupy the site of the inoculations. After careful cleansing of these vesicles the vesicular material is removed and placed in sterile glass vessels.

Preparation of the Crude Vesicular Material for use : The vesicular material is weighed and gradually triturated with twice its own weight of sterile distilled water until a fine mechanical mixture results. To this is added an additional two parts by weight of glycerine. This resultant mixture is stored at 20° F.,

small samples being taken from time to time for bacteriological and animal tests. When these tests have established the fact (1) that no extraneous pathogenic bacteria are present and (2) that the specific activity of the vaccine is high, the vaccine is considered ready for use for vaccination.

The presence of a number of non-pathogenic bacteria does not contraindicate the issue and the destruction of these is to be deprecated, as their elimination is accompanied by some degree of injury to the activity of the specific vaccine virus. Should the tests show the presence of extraneous pathogenic bacteria in the vaccine, the latter is destroyed.

Should issue of a vaccine be urgently necessary 24-48 hours after the collection of vesicular material, when animal tests would occupy too long a time, as an emergency method, chloroform vapour is passed through the vaccine and eliminated immediately. By this method all extraneous bacteria, except spores, are killed out.

The Storage of the Vaccine : As has been previously stated the virulence of vaccine depends on the presence in it of a living and highly potent specific micro-organism. The same care, therefore, has to be taken to preserve the virulence of this micro-organism as would be observed in the case of preparations of other pathogenic living micro-organisms. However great the care taken, the life and much more the pathogenicity, of any living organism must be limited, but to prolong the duration of that potency for as great a period as possible, the following two principal conditions must be rigidly observed :—

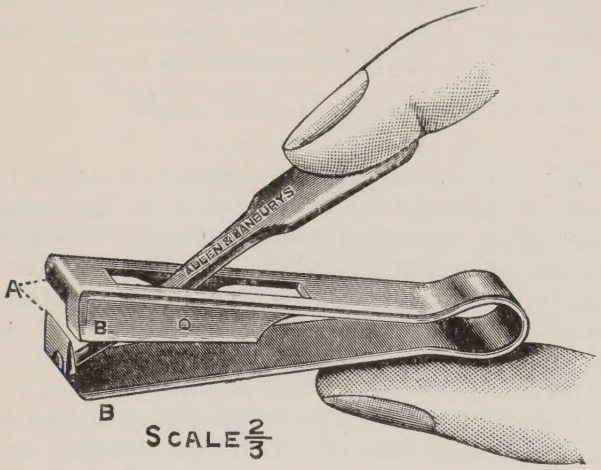
1.—The vaccine must be kept in as cold a place as possible, a temperature below 10° C. being essential. Vaccine carried on the person, placed on a shelf near a fire or any other source of heat will soon begin to deteriorate in potency. It is also highly desirable that the vaccine be not exposed to bright light.

2.—The vaccine should not be allowed to come into contact with any substance harmful to it, such as strong germicides. It is probably best to prepare the skin with sterile water before vaccinating. Vaccination should in fact be carried out as far as possible with *aseptic* rather than *antiseptic* precautions. A concentrated solution of boric acid or of biborate of soda in water may be used, however, for cleansing the skin before vaccination, as these solutions have little or no harmful effects on the specific virus.

Vaccination : Prepare the skin with sterilised water or with a saturated solution of borax.

For Glass Tubes: Remove the ends of the capillary tube by breaking the glass. Discharge the contents of the tube to the sites of inoculation by means of a mechanical blower.

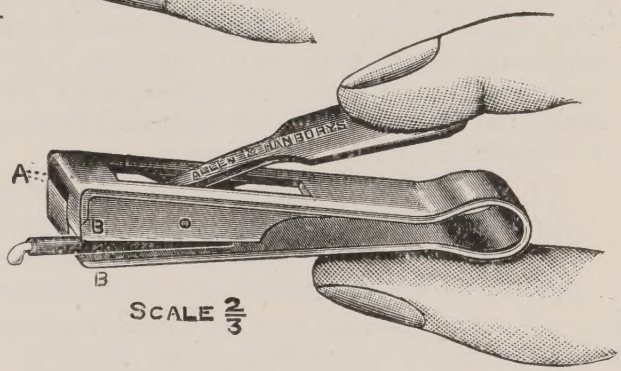
For Metal Tubes: Cut through one end of the capillary tube with the cutting edges of the special expeller, then place the tube between the compressing surfaces of the expeller and squeeze out the lymph *(see diagrams below)*.



NOTE. — The tubes should be cut just where the cylindrical shape is changing to the flattened end ; if the long axis at this point be placed perpendicularly between the cutting edges, the lumen of the tube will not be closed at the moment of cutting.

A—Cutting Edges.

B—Compressing Surfaces.



With the point of a sterile needle gently scarify the skin through the lymph at the sites of inoculation, stretching the skin slightly on each side. After the lapse of two or three minutes the excess of lymph may be wiped off the arm with some aseptic material, and the arm may be protected with an *aseptic* dressing.

Anti-Variolous vaccine is supplied in metal and also in glass capillary tubes and in bulk metal tubes for 25, 50, 100 or more vaccinations.

Veterinary Preparations.

Tuberculin.

For the diagnosis of tuberculosis the dose of Tuberculin is about 16 minims, which should be injected subcutaneously in the neck, the syringe and skin having been previously disinfected by washing with 1 in 20 carbolic lotion. The temperature of the animal should be taken just before inoculation, and also, if possible, morning and evening for two or three days previous to inoculation. The reaction consists of a rise of temperature of 1·5° to 6° F. above the average normal, occurring eight to twelve

hours after injection, and lasting twelve to fourteen hours, accompanied by some systemic disturbance. The temperature should be taken at the twentieth hour after injection, or when it can be done, at intervals from the fourth to the twentieth hour. A healthy animal is unaffected by the injection. If an animal be very extensively affected with tuberculosis the reaction may not be given, or may be masked by the febrile condition present.

Mallein.

For the diagnosis of glanders the dose of Mallein is about 16 minims, which should be injected subcutaneously in the neck at the side of the vertebræ, about midway between jaw and shoulder, the syringe and skin having been previously disinfected by washing with 1 in 20 carbolic lotion. Before the inoculation, the morning and evening temperatures of the animal should be taken at least once, and if possible more frequently. It is often convenient to record the temperature in the morning and again in the evening, say at eight or nine o'clock, immediately before inoculating the animal, in which case the phenomena which are important for the diagnosis occur from 8 or 9 a.m. to 8 or 9 p.m. on the following day. The temperature should be taken at the ninth, twelfth, fifteenth and twentieth hours after the inoculation. A complete reaction comprises :—

1.—A rise of temperature of more than 2½° F. The temperature usually reaches its maximum from the twelfth to the fifteenth hour, more rarely on the nineteenth and twentieth hour after the inoculation.

2.—The formation of an extensive, hot and painful swelling at the site of inoculation. The swelling varies from the size of the palm of the hand to four or five times this area. It increases in size until the twelfth to the fourteenth hour after the inoculation, and then remains stationary for two or three days. The swelling disappears in five to eight days.

Systemic disturbance such as prostration, loss of appetite, shivering, etc., may occur. These symptoms, when present, are more or less persistent. The temperature reaction is unreliable in all cases in which the temperature at time of inoculation is 2·5° F. above normal. In such cases, if there are any suspicious clinical signs to assist, reliance may be placed on the occurrence of the local swelling.

Tetanus Antitoxin.

The observations of British, American, French, and German veterinarians, extending over many thousands of cases, have definitely proved that an adequate dose of tetanus antitoxin, given immediately or even shortly after wounds or operations, is a certain preventive against the subsequent occurrence of tetanus. Tetanus Antitoxin (Veterinary) is supplied in bottles of 1,500 units each, a quantity which clinical experience has shown to be an adequate prophylactic dose.

Antitoxins, Sera, Vaccines, etc.

PREPARED BY

THE LISTER INSTITUTE.

Regular orders for Sera and Vaccines should be sent to Messrs. Allen & Hanburys Ltd., Bethnal Green, E.2.

Telegraphic Address—"Greenburys Edo London."
Telephone No.—Bishopsgate 1122 (6 lines).

On Sundays, Public Holidays, Saturdays after 12.30 p.m., and other days after 5.30 p.m., Telegrams and Telephone Messages may be sent to Messrs. Allen & Hanburys Ltd., 7 Vere Street, W.1. Telegraphic Address—"Vereburys Wesdo London."
Telephone No.—Mayfair 2216 (3 lines).

If more than one phial or case be required, numerals should be used after the Code Word.

MODES OF DESPATCH.

(1) If not instructed otherwise, will be sent by post.
*(2) If by post, with express delivery from Post Office of destination, add "Express" to Code Word.
*(3) If by first passenger train, entailing messenger boy to London terminus, add "Passenger" to Code Word.
*(4) If by special messenger to destination, by train or omnibus, add "Special" to Code Word.

* *Out-of-pocket expenses for delivery will be charged.*

Therapeutic Sera

Telegraphic Code		
Concentrated Diphtheria Antitoxin		
Inter	In phials of 500 units, in 2 c.c.	1/6
Alpha	„ „ 1,000 units, in 2 c.c.	2/-
Spondaios	„ „ 2,000 units, in about 2 c.c.	3/6
Preter	„ „ 4,000 units, „ 5 c.c.	7/-
Karma	„ „ 6,000 units, „ 6 c.c.	9/6
Rota	„ „ 8,000 units, „ 8 c.c.	10/6
Rotos	„ „ 10,000 units, „ 10 c.c.	12/6
List	„ „ 16,000 units, „ 16 c.c.	20/-
Concentrated Tetanus Antitoxin		
Ante	In phials of 500 units, in about 2 c.c.	1/6
Lambda	„ „ 1,500 units, in not more than 5 c.c.	4/-
Ro	„ „ 8,000 units, in not more than 12 c.c.	20/-
Prevent	„ „ 20,000 units, in not more than 25 c.c.	45/-
Concentrated Scarlet Fever Antitoxin		
Scarlet	In phials of 10 c.c.=40 c.c. unconcentrated	10/6
Anti-Dysentery Serum (multivalent) Refined		
Theta	In phials of 20 c.c.	7/6
Anti-Dysentery Serum (multivalent) Concentrated		
Bariah	In phials of 5 c.c.=40 c.c. unconcentrated	14/6
Chaseba	„ „ 10 c.c.=80 c.c. „	28/-
Gerasa	„ „ 25 c.c.=200 c.c. „	69/-
Anti-Gonococcus Serum (multivalent)		
Astral	In phials of 10 c.c.	3/6
Gemini	„ „ 25 c.c.	8/6

Telegraphic Code		
	Anti-Meningococcus Serum (multivalent)	
Meningo	In phials of 10 c.c.	3/6
Ektos	„ „ 15 c.c.	5/-
Hamza	„ „ 30 c.c.	10/-
	Anti-Plague Serum, Refined	
Gamma	In phials of 20 c.c.	7/6
	Anti-Pneumococcus Serum	
Dharma	In phials of 10 c.c.	4/-
Pneum	„ „ 25 c.c.	8/6
	Anti-Scorpion Serum (multivalent) Concentrated	
Juxta	In phials containing a dose to neutralize one sting	5/-
	Anti-Staphylococcus Serum (multivalent)	
Deva	In phials of 10 c.c.	3/6
Prana	„ „ 25 c.c.	8/6
	Anti-Streptococcus Serum (multivalent)	
Beta	In phials of 10 c.c.	3/6
Inst	„ „ 25 c.c.	8/6
	Normal Serum (Horse)	
Pente	In phials of 10 c.c.	1/6
Ute	„ „ 25 c.c.	3/-
	"Schick Test" Solutions	
Infra	Diphtheria toxin solution } Dose 0·2 c.c. in phials of 1 c.c. Control Solution } per set	2/6
Circa	Ditto ditto ditto 0·2 c.c. in phials of 5 c.c. per set	6/-
	Diphtheria Prophylactic	
	Diphtheria toxin-antitoxin mixture (for active immunisation only)	
Cis	In phials of 1 c.c.	2/6
Extra	„ „ 5 c.c.	10/-

Bacterial Vaccines

Acne Vaccine

In phials each containing per c.c. respectively :—

Korus	(*a*) Green.	*Staphylococcus aureus*	250 million
		Bacillus acnes	10 million
			per phial 2/6
Agon	(*b*) Mauve.	*Staphylococcus aureus*	500 million
		Bacillus acnes	20 million
			per phial 2/6
Phronimos	(*c*) White.	*Staphylococcus aureus*	125 million
		Bacillus acnes	125 million
			per phial 2/6
Daktos	(*d*) Amber.	*Staphylococcus aureus*	250 million
		Bacillus acnes	250 million
			per phial 2/6
Potos	(*e*) Blue.	*Staphylococcus aureus*	500 million
		Bacillus acnes	500 million
			per phial 2/6
Ob	(*f*)	*Bacillus acnes* (alone)	10 million
			per phial 2/6

Compound Catarrhal Vaccine

Trans	In phials containing 235 million organisms per c.c.	2/6
Pone	„ „ 470 „ „ „	2/6
Post	„ „ 940 „ „ „	2/6
Propter	„ „ 1,880 „ „ „	2/6

Telegraphic Code		
	M. catarrhalis Vaccine	
Apud	.. In phials containing 25 million organisms per c.c.	2/6
Jonos	.. „ „ 50 „ „ „	2/6
Agathaos	.. „ „ 100 „ „ „	2/6
Ennatos	.. „ „ 250 „ „ „	2/6
	Cholera Vaccine (multivalent)	
Eta	.. In phials containing 10,000 million organisms per c.c.	2/6
	Coley's Fluid	
Delta	.. In phials of 2 c.c.	7/6
	Gonococcus Vaccine	
Tetartos	.. In phials containing 5 million organisms per c.c.	2/6
Mikros	.. „ „ 10 „ „ „	2/6
Seba	.. „ „ 50 „ „ „	2/6
Arba	.. „ „ 100 „ „ „	2/6
Wahid	.. „ „ 300 „ „ „	2/6
	Compound Influenza Vaccine	
Contra	.. In phials containing 330 million organisms per c.c.	2/6
Clam	.. „ „ 660 „ „ „	2/6
	Plague Vaccine (3,000 million organisms per c.c.)	
Cora	.. In phials of 1 c.c.	2/6
Phulax	.. „ „ 5 c.c.	7/6
Soma	.. „ „ 10 c.c.	15/-
Zeta	.. „ „ 20 c.c.	20/-
	Pneumobacillus (Friedlaender) Vaccine	
Pentakis	.. In phials containing 50 million organisms per c.c.	2/6
Subter	.. „ „ 100 „ „ „	2/6
Erga	.. „ „ 200 „ „ „	2/6
	Pneumococcus Vaccine (multivalent)	
Duo	.. In phials containing 5 million organisms per c.c.	2/6
Mala	.. „ „ 10 „ „ „	2/6
Hapax	.. „ „ 50 „ „ „	2/6
Seta	.. „ „ 100 „ „ „	2/6
	S. Rheumaticus Vaccine	
Ek	.. In phials containing 5 million organisms per c.c.	2/6
Do	.. „ „ 10 „ „ „	2/6
Tien	.. „ „ 25 „ „ „	2/6
Char	.. „ „ 50 „ „ „	2/6
Thalatha	.. „ „ 100 „ „ „	2/6
Thamanya	.. „ „ 200 „ „ „	2/6
	B. Septus Vaccine	
Citra	.. In phials containing 100 million organisms per c.c.	2/6
Palam	.. „ „ 200 „ „ „	2/6
Hebdomos	.. „ „ 400 „ „ „	2/6
	Staphylococcus Vaccines	
	(*a*) Made with *Staphylococcus aureus* alone, for furunculosis and sycosis	
Philos	.. In phials containing 500 million organisms	2/6
Nu	.. „ „ 1,000 „ „	2/6
Pemptos	.. „ „ 2,000 „ „	2/6
	(*b*) Made with mixed cultures of *Staphylococcus aureus, citreus* and *albus*, for acne	
Okto	.. In phials containing 500 million organisms	2/6
Pi	.. „ „ 1,000 „ „	2/6
Melas	.. „ „ 2,000 „ „	2/6
	(*c*) Made with *Staphylococcus albus* alone	
Kakos	.. In phials containing 500 million organisms	2/6
Treis	.. „ „ 1,000 „ „	2/6
Coronus	.. „ „ 2,000 „ „	2/6

Telegraphic Code		
	Streptococcus Vaccine (multivalent)	
Tessares	.. In phials containing 5 million organisms per c.c.	2/6
Hepta	.. „ „ 10 „ „ „	2/6
Dodeka	.. „ „ 20 „ „ „	2/6
Sub	.. „ „ 50 „ „ „	2/6
Supra	.. „ „ 100 „ „ „	2/6
	Typhoid and Paratyphoid Vaccine (T.A.B.)	
Typa	In phials containing per c.c.	
	B. typhosus .. .. 1000 million	
	B. paratyphosus A. .. .. 750 million	
	B. paratyphosus B. .. .. 750 million	
	per phial	2/6
	Typhoid, Paratyphoid and Cholera Vaccine	
Bait	In phials containing per c.c.	
	B. typhosus .. .. 1000 million	
	B. paratyphosus A. .. .. 750 million	
	B. paratyphosus B. .. .. 750 million	
	V. choleræ .. .. 10,000 million	
	per phial	2/6
	Typhoid Vaccine	
Omicrom	.. In phials containing 1,000 million organisms per c.c. per phial	2/6

Bacterial Vaccines also supplied in rubber-capped bottles .. 10 c.c. 15/- ; 20 c.c. 22/6 ; 25 c.c. 25/-

Anti-Variolous Vaccine

Anti-Variolous Vaccine (Calf Lymph)

Chimetal	.. Metal capillary tubes (one vaccination) .. each 8d., per doz.	7/-
Chiglass	.. „ „ „ „ „ .. „ 8d. „	7/-

(Glass tubes sent unless otherwise stated.)

Veterinary Preparations

Tetanus Antitoxin (Veterinary)

Sigma	.. In phials of 1,500 units	3/-
	Mallein	
Tau	.. In phials of 3 c.c.	1/6
	Tuberculin	
Omega	.. In phials of 3 c.c.	1/6

All prices net.

Instructions as to the use of each preparation are issued with every tube or case.

SOLE WHOLESALE AGENTS:

Allen & Hanburys Ltd., London

City House: 37 Lombard Street, E.C. 3.

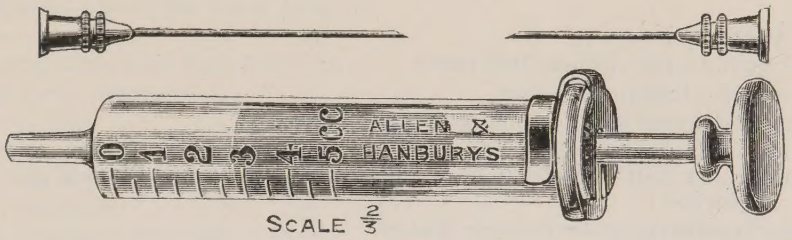
West End House: 7 Vere Street, W. 1.

The Preparations can also be obtained at the undermentioned Special Provincial Depots:

ABERDEEN—Davidson & Kay.
BRISTOL—Ferris & Co.
BELFAST—McMullan & Co.
BIRMINGHAM—Southall Bros. & Barclay,
BOURNEMOUTH—G.E.Bridge & Co. [Ltd.
CAMBRIDGE—Church & Son.
DUBLIN—Fannin & Co., Ltd.
EDINBURGH—Duncan, Flockhart & Co.
GLASGOW—T. & H. Smith, Ltd.
ISLE OF WIGHT—W. T. Deeks, Shanklin.
JERSEY—P. Le Quesne.
LEEDS—Reynolds & Branson, Ltd.
LINCOLN—Battle, Son & Maltby.
LIVERPOOL—Clay & Abraham.
MANCHESTER—James Woolley, Sons & Co. Ltd.
NEWCASTLE—Brady & Martin, Ltd.
NORWICH—King & Co.
NOTTINGHAM—C. A. Bolton.
OXFORD—Cousins, Thomas & Co.
SHEFFIELD—G. T. W. Newsholme,
YORK—Raimes & Co. [Ltd

All-Glass Serum Syringe

BEST QUALITY



SCALE $\frac{2}{3}$

In metal case

	With 2 steel needles
3 c.c.	8/6
5 c.c.	10/6
10 c.c.	12/6
20 c.c.	16/6

Glass syringe without case or needles

3 c.c. .. 6/- 5 c.c. .. 7/6 10 c.c. .. 8/6 20 c.c. .. 12/-

New needles for above

	Steel	Platinum-iridium
3 c.c.	9d. each	from 4/6 each
5 c.c.	1/- „	„ 6/- „
10 c.c.	1/3 „	„ 6/- „
20 c.c.	1/3 „	„ 6/- „

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